IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
Timothy MURPHY	Art Unit: 2728
Application No.: 10/770,403	Examiner: Prebilic, Paul B.
Filing Date: 4 February 2004	Attorney Ref. No.: 010-001
For: Methods for Treating Obesity	**Via EFS-Web**

BRIEF FOR APPELLANT

Mail Stop APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMES NOW APPELLANT to present this Brief in support of the appeal of the final rejection of Claims 1, 3-6, 8-14, and 23-25 in the above-captioned patent application. The Notice of Appeal having been timely filed on 30 July 2008, this Brief is due to be filed on 30 November 2008, with the concurrently filed Petition for a two-month extension of time. 37 C.F.R. §§ 1.7(a), 41.37 (a)(1), (e).

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. If, however, additional extensions of time are necessary to prevent abandonment of this application or dismissal of this appeal, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to Deposit Account 50-2821.

For the following reasons, Appellant respectfully submits that the final rejection of each of Claims 1, 3-6, 8-14, and 23-25 in this application is in error, and therefore respectfully requests reversal of the rejections.

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I. REAL PARTY IN INTEREST

The real party in interest in this application is Timothy Murphy, MD, the sole inventor.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences related to this application or appeal.

III. STATUS OF CLAIMS

All of the pending claims, Claims 1, 3-6, 8-14, and 23-25, stand finally rejected in the Office Action dated 30 April 2008 ("Office Action"); Claims 2, 7, and 15-22 have been cancelled. The rejection of all of Claims 1, 3-6, 8-14, and 23-25 is the subject of this appeal.

IV. STATUS OF AMENDMENTS

All amendments to the claims have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

This application describes and claims unique methods and devices embodying principles of the invention. As Appellant has used paragraph numbering in his specification, reference will be made to portions of the specification using that numbering convention.

Claim 1: According to one method embodying principles of the present invention, a method of treating morbid obesity in a patient comprises reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient, including placing a blood flow reducing device inside an artery that carries blood to the small intestine (Fig. 1; paragraphs [0046] - [0048], [0053], [0055]).

Claim 14: According to another method embodying principles of the present invention, placing comprises placing an endograft (Fig. 1, 100) inside the artery (Fig. 1, A), the endograft including a first portion (Fig. 1, 102) having a size selected to hold the endograft in place in the artery, and a second portion (Fig. 1, 106) smaller than the first portion that reduces blood flow through the artery, and including adjusting the second portion of the endograft to achieve a pressure change within a desired range so that abdominal pain not related to meals does not occur (paragraphs [0050], [0053]).

Claim 23: According to another method embodying principles of the present invention, a method of treating morbid obesity in a patient comprises permanently reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient (Fig. 1; paragraphs [0046] - [0048], [0053], [0055]).

Claim 24: According to yet another method embodying principles of the present invention,a method of treating morbid obesity in a patient comprises reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, a fixed, invariable amount in the patient (Figs. 1, 4b; paragraphs [0046] - [0048], [0053], [0055]).

Claim 25: According to a further method embodying principles of the present invention, a method of treating morbid obesity in a patient comprises continuously reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient for a time effective to reduce the patient's weight (Figs. 1, 4b; paragraphs [0046] - [0048], [0053], [0055]).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed in this appeal are:

(a) The rejection of Claims 1, 3-6, and 8-14 under 35 U.S.C. § 103(a) over U.S. Published Patent Application No. 2002/0161414, invented by Flesler *et al.* ("Flesler), in view of U.S. Patent No. 6,120,534, issued to Ruiz and U.S. Patent No. 5,690,644, issued to Yurek.

(b) The rejection of Claims 23-25 under either 35 U.S.C. § 102(b), as being anticipated by *Flesler*, or, in the alternative under 35 U.S.C. § 103(a), as being obvious over *Flesler* in view of *Ruiz*.

VII. ARGUMENTS

A. Introduction

Beginning at page 2 of the Office Action, Claims 1, 3-6, 8-10, and 12-14 were rejected under 35 U.S.C. § 103(a) as reciting subject matters that are allegedly obvious, and therefore allegedly unpatentable, over *Flesler* in view of *Ruiz*, for the reasons presented at pages 2-4. Beginning at page 4, Claim 11 was rejected under 35 U.S.C. § 103(a) as reciting subject matter that is allegedly obvious, and therefore allegedly unpatentable, over *Flesler* and *Ruiz* and further in view of *Yurek*, for the reasons presented at page 4. Beginning at page 4 of the Office Action, Claims 23-25 were rejected under 35 U.S.C. § 102(b) as reciting subject matters that are allegedly identically disclosed in *Flesler* or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over *Flesler* in view of *Ruiz*. For at least the following reasons, these rejections are in error and should be reversed.

Claims 1, 3-6, and 8-13 stand or fall together.

Claim 14 stands or falls alone.

Claim 23 stands or falls alone.

Claim 24 stands or falls alone.

Claim 25 stands or falls alone.

To simplify consideration of the rejection, the prior art relied upon in the Office Action will be discussed after a brief review of the law of obviousness under section 103.

B. Legal Standards

Claim construction begins with the words of the claims. *Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971 (Fed. Cir. 1999). Claim language should be interpreted as one reasonably skilled in the art would have interpreted the claim at the time of the patent application date. *Vivid Techs., Inc. v. American Science & Engineering, Inc.*, 200 F.3d 795, 804

(Fed. Cir. 1999); *Wiener v. NEC Elec., Inc.,* 102 F.3d 534, 539 (Fed. Cir. 1996). Where the claim term has no specialized meaning to persons of skill in the art, the ordinary meaning of the words to those of ordinary skill in the art controls, unless the evidence indicates that the inventor used them differently. *Karlin*, 177 F.3d at 971. Such evidence includes the specification and prosecution history, both of which must be analyzed to determine if the inventor limited or redefined any of those terms. *Watts v. XL Sys., Inc.*, 232 F.3d 877, 882-84 (Fed. Cir. 2000); *Vivid Techs.*, 200 F.3d at 804. If claim language is not clear on its face, then intrinsic evidence also should be consulted to resolve the lack of clarity. *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001).

A patent claim is invalid for obviousness if the differences between the claimed subject matter and the prior art are such that the claimed subjected matter as a whole would have been obvious at the time of the invention to a person of ordinary skill in the relevant art. 35 U.S.C. § 103(a). The determination of obviousness is a legal conclusion based on underlying factual considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). These factual inquiries include: the scope and content of the prior art; the differences between the prior art and claims at issue; the level of ordinary skill in the pertinent art; and objective evidence of nonobviousness (*i.e.*, secondary considerations). *Graham*, 383 U.S. at 17; *KSR International Co. v. Teleflex Inc. et al.,* 550 U.S. ___, No. 04-1350, slip op. at 2 (April 30, 2007); *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc.*, 229 F.3d 1120, 1124 (Fed. Cir. 2000); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co.*, 464 F.3d 1356 (Fed. Cir., 2006).

It is against this factual background that the ultimate determination of obviousness is made, *i.e.*, the claimed invention is obvious if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. 35 U.S.C. § 103(a). "In line with th[e] statutory standard [of 35 U.S.C. §103], [the] case law provides '[t]hat consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of

success, viewed in light of the prior art.' Two requirements are contained in this criterion." *Brown & Williamson Tobacco Corp.*, 229 F.3d at 1124 (*quoting In re Dow Chem.*, 837 F.2d 469, 473 (Fed. Cir. 1988)).

The U.S. Supreme Court recently addressed the obviousness of a combination of known elements. Although a rigid application of the Court of Appeals for the Federal Circuit's "teaching, suggestion, or motivation" ("TSM") test was rejected, the Court stated that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR, slip op.* at 12. For example, the Court explained, when the prior art elements work together in an unexpected and fruitful manner, a finding of non-obviousness is supported. *Id.* (*citing United States v. Adams,* 383 U.S. 39, 40 (1966)). If, however, the combination of old elements does no more than they would in separate, sequential operation, even though the combination might perform a useful function, the combination is likely obvious. *Id.* at 13 (*citing Anderson's-Black Rock, Inc. v. Pavement Salvage Co.,* 396 U.S. 57 (1969)). Finally, the Court stated that "[i]f a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." *Id.* (*citing Sakraida v. AG Pro, Inc.,* 425 U.S. 273 (1976)). Nevertheless, the Court in *KSR* still required that there be a reason or purpose for modifying the prior art to arrive at the claimed invention, in order to find the claimed subject matter unpatentable under section 103(a). *Id.* at 14-15 ("Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.").

Thus, while the Supreme Court in *KSR* ruled that the requirement, in the jurisprudence of the Court of Appeals for the Federal Circuit, for a "teaching, suggestion, or motivation" to make up for the deficiencies in the prior art to meet the claimed invention, cannot be rigidly applied, the Federal Circuit had already articulated that its test was flexible. *See*, *e.g.*, *DyStar Textilfarben*, 464 F.3d at 1367 ("Our suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense") (emphasis in

original); *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006) ("There is flexibility in our obviousness jurisprudence because a motivation may be found *implicitly* in the prior art. We do not have a rigid test that requires an actual teaching to combine . . .".) (emphasis in original). It is therefore plain that *KSR* did not reject the TSM test, but only its rigid application to the facts before the Court in that case, and it is thus still a requirement for a rejection under section 103 during *ex parte* prosecution of a patent application, that there be some rational reason articulated by the PTO why a person of ordinary skill in the art would modify the prior art to arrive at the claimed invention. *Accord Ex parte Catan*, ___ U.S.P.Q. ___, Appeal No. 2007-0820, slip op. at 11 (U.S.P.T.O. Brd. Pat. App. & Int., July 3, 2007) (*quoting In re Kahn*, 441 F.3d 977, 988, (Fed. Cir. 2006)) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"); *id.*, slip op. at 19-21 (articulating motivation to modify one prior art device to arrive at the claimed invention).

C. The prior art

(i) *Flesler*

Flesler describes systems and methods allegedly useful for treating obesity in a patient. Appellant reproduces herein Figs. 3a, 3b, and 4 from *Flesler* to assist in a better understanding of its disclosure. *Flesler* uses intermittent electrical stimulation on the exterior of "or in the vicinity of" (para. [0113]) the superior mesenteric artery 110 to intermittently narrow the mesenteric arteries, only after meals. Figs. 3a and 3b illustrate the waveforms of the electrical impulses that *Flesler* discloses. Because *Flesler* applies electrical stimulation to the muscle cells of the artery, whatever constriction *Flesler* may be able able to achieve, by electrically stimulating contraction of these muscles, can't be controlled. That is, the amount of narrowing occurring in the arteries would not be apparent to any observer, may be more than is safe (leading to clotting or acute blockage of the arteries with a high risk of bowel infarction/death and patient death), or less than is necessary to achieve the goal of incomplete absorption or hindered digestion. Stated somewhat differently, the amount of narrowing of the artery by electrical stimulation is not consistent and reproducible. *Flesler* acknowledges and prefers that any reduction in the blood flow through the artery is discontinuous, variable, and not permanent: "The constriction produced by apparatus 118 preferably transiently and controllably reduces the blood flow to small intestine 120. . .". Para. [0113].

FIG. 3B

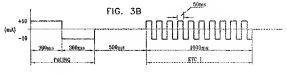


FIG. 3C

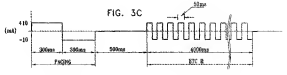
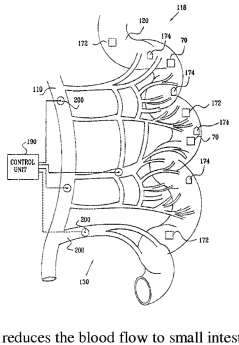


FIG. 4



Flesler also emphasizes that his methods are to be used only with meals, and are not permanent solutions:

> Alternatively or additionally, operation of apparatus 118 is initiated or supplemented responsive to a parameter of the contents of small intestine 120, such as an indication by sensors 172 of the lipid concentration thereof. Further alternatively or additionally, the patient is enabled to activate apparatus 118 (e.g., during and after eating dessert, or for a determined time period when the patient is going to sleep) and to deactivate the apparatus (e.g., when the patient has a headache, or has orally taken a medication). Still further alternatively or additionally, apparatus 118 is activated a fixed or variable time (e.g., 10-30 minutes) following initiation of a meal, when it is expected that some digestive products will have reached the small intestine.

Para. [0116].

Furthermore, the Office Action acknowledges that *Flesler*'s method is performed exterior to the artery; at page 3, the Office Action states that *Flesler*'s devices are placed around the artery.

(ii) *Ruiz*

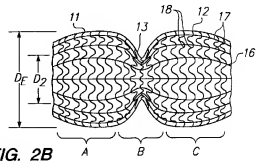


FIG. 2B

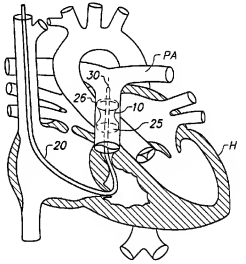


FIG. 4A

Ruiz describes a blood flow restriction stent; Figs. 2B and 4A are reproduced to the right herein to assist in a better understanding of *Ruiz*'s disclosure. The stent 10 (see Fig. 2B) has an adjustable internal diameter. The stent 10 is installed in the pulmonary artery PA of a patient. The reduced inner diameter D2, at section 13, reduces blood flow through the stent 10 and, therefore, through the artery in which it is installed. *Ruiz* discusses the problems associated with prior methods of reducing blood flow in the pulmonary artery, including "pulmonary artery banding", in order to combat congenital cardiac malformations which cause overloading of the pulmonary circulation. See *Ruiz*, column 1, lines 11-51. The devices and methods described in Ruiz are restricted to treatment of overloading of the pulmonary circulation, which can reduce distal pulmonary pressure. While *Ruiz* describes several methods of using the stents, all of the descriptions in *Ruiz* are restricted to a highly specialized placement to reduce distal pressure in the pulmonary circulation. *See* column 4, line 43 through column 5, line 24; column 6, lines 28-61; and column 7, lines 30-60. Nowhere does *Ruiz* disclose or describe anything relating to placement of the device in any other vessel in the human body, or treatment of any malady other than congenital cardiac malformations which cause overloading of the pulmonary circulation.

(iii) *Yurek*

Yurek describes an apparatus 16 useful for deploying a stent 10 in the vasculature of a patient. *Yurek* does not disclose, describe, or relate to the treatment of obesity.

D. The subject matters of Claims 1, 3-6, 8-14, and 23-25 are patentable over the prior art

This application describes examples of methods and devices embodying principles of the present invention. As described at length in this application, long term, fixed, internal reduction of blood flow to the small intestine of a patient can reduce the function of the small intestine to digest food, thereby reducing the caloric intact possible from that food. As mentioned in this application, obesity can be affected by vascular procedures because weight loss is associated with chronic mesenteric ischemia. By placing a narrowing, partial blockage, stenosis, or blood-flow restrictor into an artery that supplies blood to the duodenum, the lower intestine, jejunum, ileum, or combinations thereof, mesenteric ischemia can be induced. The blood flow through arteries that are collateral to the superior mesenteric artery, *e.g.*, the gastroduodenal and inferior mesenteric arteries, is optionally also reduced, so that collateral blood flow does not make up for the blood flow reductions in the superior mesenteric artery. While these organs typically have more than one blood supply, restriction of the blood supply by forming a partial blockage in one or more select arteries can induce mesenteric ischemia, thus reducing the effectiveness of the organ to digest food, and consequently reducing the patient's intake of compounds from the food the patient has ingested.

Appellant presents his arguments in the same order as the rejections levied in the Office Action.

(i) Rejections under 35 U.S.C. § 103(a)

(a) Claims 1, 3-6, and 8-13

Appellant and the undersigned interviewed with Mr. Prebilic on this application on 5 June 2007. The interview began with Dr. Murphy briefly discussing the subject matter described and claimed in this application, to wit, methods useful for treating morbid obesity in patients. Dr. Murphy continued by explaining that Dr. Murphy had twice applied to the National Institutes of Health, specifically the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Biomedical Imaging and Bioengineering, for grants to further study and develop the subject matter described and claimed in this application. Appellant submitted copies of those NIH grant applications; copies are presented with this Brief's Evidence Appendix. During the interview, Dr. Murphy presented to Mr. Prebilic copies of the NIH's responses to those grant requests, copies of which are also appended hereto.

The two NIH grant responses bear directly on the positions stated in the Office Action because they are objective evidence of non-obviousness of the claimed subject matters. During the interview, the undersigned emphasized to Mr. Prebilic that the NIH grant responses are evidence of non-obviousness different in kind from the sorts of 'evidence' often submitted in patent applications, because the NIH grant responses: (1) were prepared by a U.S. government agency not concerned with patentability, but instead with safety and public health; (2) were signed by a panel of experts in the medical fields with which the technology deals, which experts have no connection with Dr. Murphy or this patent application; (3) were not solicited in order to respond to the Office Action and its rejections; and (4) essentially state that the claimed methods, as embodied in the experimental protocols described in the NIH grant applications, were not only noted to be "highly innovative", but were felt to be so unconventional that they were considered by several reviewers to be both unsafe and unethical.

The NIH grant responses are strong evidence of non-obviousness of the claimed methods. As discussed above, the NIH grant responses include discussions by true experts in the field of

Dr. Murphy's methods and the effects in patients that the methods would have. Appellant points out that these impartial experts repeatedly commented in the NIH grant responses that Dr. Murphy's methods are 'novel' and 'innovative'. More importantly with respect to the non-obviousness of the claimed methods, both of the NIH grant responses caution against the practice of the methods which, in the experts' opinions, would cause severe pain and 'food fear' in the patients. Indeed, several of the comments in the NIH grant responses go so far as to suggest that performing these methods may be medically 'unethical'. Thus, in essence, the panels of experts assembled by the NIH to assess Dr. Murphy's grant applications on the claimed methods fail to see how the treatment could possibly be effective, and rather are strongly of the opinion that a person of ordinary skill in this art should not perform the methods that are currently claimed, based on their extensive and deep knowledge and experiences in exactly the fields of Dr. Murphy's endeavors.

Therefore, the NIH grant responses indicate that the medical community concerned with Dr. Murphy's invention, including those of ordinary skill in the art to which these inventions pertain, does not at all find Appellant's claimed methods to be obvious and, strongly to the contrary, are of the opinion that the treatment proposed is radical or even outrageous to consider. Thus, the evidence in this record strongly shows that a person of ordinary skill in the art, at the time of Appellant's invention, would not be motivated to perform the methods recited in the pending claims and, indeed, would likely find them implausible, contrary to their medical knowledge, and abhorrent.

In an Advisory Action dated 23 July 2007 ("Advisory"), Mr. Prebilic opined on a Continuation Sheet:

> The argument pertain [sic] to the new evidence that was not filed in response to a new rejection of the Final Office action. A cursory review of the evidence suggests that the experts were not aware of the patent to Flesler and their knowledge of patents may not be comparable to one of ordinary skill in the art.

With regard to the statement that "the evidence suggests that the experts were not aware of the patent of Fesler and their knowledge might not be comparable to one of ordinary skill in the art", it is certainly true that the individuals who make up the panel of experts are not patent examiners. Indeed, these persons are selected because of their knowledge and experience in their fields, and are assembled to evaluate the technical subject matter for which a grant is requested. Then, Mr. Prebilic stated that these experts are not persons of ordinary skill in the art.

On the contrary, however, the individuals who make up the review panel are selected precisely because of their knowledge and expertise in the field, and therefore are at least as skilled and knowledgeable as the hypothetical 'person of ordinary skill in the art'. It should be particularly noted that the pending claims are directed to *methods* for treating a patient, which is significantly different subject matter from *devices* which are intended to be used to treat a patient, and carry with them entirely different, and higher, levels of skill in the routineer in the art. The experts on the review panel give a measure of that skill and, at worst, are each merely of ordinary skill in their arts. Considering that they are each appointed by the U.S. government to review grant proposals, among other things to safeguard public safety (which is not at all an issue with which the PTO is concerned), it is plainly the case that these individuals are more skilled and knowledgeable in their fields than the ordinary routineer.

Thus, the panel of true experts, and not of mere routineers in the art, views the invention claimed herein as novel, risky, and even outrageous conceptually. With such as view, Appellant respectfully submits that the lowlier 'person of ordinary skill in the art' would be even more adverse to the claimed methods, and would certainly not look to make the *Flesler* method more permanent, fixed, and/or invariable than *Flesler*'s electroshock process already is. Stated somewhat differently and rhetorically, if even a panel of hyper-skilled experts in the field finds the claimed invention to be novel, how is it that the person of ordinary skill in the art would nevertheless find it to be obvious? The answer to that question is, in the final analysis, quite simple: the claimed *methods* are not obvious variants of the *Flesler* procedures, as evinced by the views of the panel of experts.

The only remaining reason why one would modify *Flesler* in view of *Ruiz*, as alleged in the Office Action to be obvious, is upon an impermissible hindsight reconstruction of the claimed invention from Appellant's own specification, and therefore a *prima facie* case of obviousness has not been made.

The Office Action included a derision of the qualifications of the NIH's panel of experts, appearing at the bottom of page 5, which is plainly inappropriate. Because Mr. Prebilic has questioned their qualifications, however, Appellant located (via public, internet searches) evidence of the level of skill of the members of the NIH panel. Appellant thus filed fifteen (15) biographies, curricula vitae (CV), or the like, one for each of the panelists; copies of that evidence is also attached hereto at this Brief's Evidence Appendix. While Appellant will not belabor the record by going through each of them in detail, a brief review of each plainly demonstrates that each of the NIH panelists is certainly of at least ordinary skill in the art(s) to which this application's claims relate and, more likely, are of skill higher than that of the routineer in these arts. As Appellant has repeatedly asserted in this record, the opinion of the panelists, thrice documented in this record, is that a person of ordinary skill in the art would be strongly motivated not to perform the claimed methods.

Mr. Prebilic's logic is backwards concerning the relevance of the NIH's grant assessment to the patentability of the claimed methods. Mr. Prebilic draws fault with the fact that there is no evidence that the panel of experts evaluated the *Flesler* and *Ruiz* documents when making their evaluation of the safety and efficacy of Dr. Murphy's proposed methods; however, this concern is completely backwards, and entirely misses the point. Mr. Prebilic alleges that all of the claimed method steps are cumulatively disclosed in *Flesler* and *Ruiz*, the same method steps that are discussed at length in Dr. Murphy's grant proposals, and then alleges that the panel of experts did not evaluate what Mr. Prebilic says is in the prior art.

Therefore, assuming *arguendo* that Mr. Prebilic is correct (that *Flesler* and *Ruiz* together describe all of the steps in the claimed methods), and noting that the grant proposals describe the claimed methods, it necessarily follows that the panel of experts would have been evaluating the hypothetical combination of *Flesler* and *Ruiz*. Thus, according to Mr. Prebilic's logic, the NIH

panelists in fact were evaluating the hypothetical combination of *Flesler* and *Ruiz* when they gave their negative evaluations.

Furthermore, it is exactly because the panel of experts was not evaluating patentability that makes their assessment so powerful, and relevant. Again assuming *arguendo* that *Flesler* and *Ruiz* together describe all of the steps in the claimed methods, the same methods that are described in Dr. Murphy's grant requests, then it is abundantly clear that the panel of experts' opinion is that the hypothetical combination of *Flesler* and *Ruiz* is novel, risky, and even outrageous - that is, non-obvious. Mr. Prebilic makes the fundamental mistake of assuming that a person of ordinary skill in the art of medical methods would evaluate a new method for patentability, rather than what physicians actually evaluate them for: safety and efficacy. Thus, Mr. Prebilic's opinion is that a physician of ordinary skill in the art would combine the method steps of *Flesler* and *Ruiz* in order to arrive at Dr. Murphy's claimed combinations, and turns a blind eye to the untainted evidence that real experts in the field, not merely persons concerned with patentability such as Mr. Prebilic and the undersigned, find Dr. Murphy's proposed methods so novel and unusual that they believe the proposed *methods* outrageous.

There are numerous other clear errors in Mr. Prebilic's evaluation of the NIH documents:

(1) Mr. Prebilic questions the level of skill of the panel experts, because it is allegedly not clear which of them evaluated Dr. Murphy's proposal. Appellant thus has provided the evidence in the record to establish that they are at least of ordinary skill, and the inclusion of each one of them on the panel by the NIH plainly indicates that they are experts in the applicable field.

(2) Mr. Prebilic faults the evidence for not being in affidavit form; while true, the NIH documents are just as relevant as Mr. Prebilic's opinion, despite the fact that he also has not executed a Declaration to present his opinion as a U.S. government official, which is exactly what is each of the members of the panel of experts. Also, there are no grounds for those who volunteer to provide peer review for grant applications to be less than honest in giving their opinions. Furthermore, Mr. Prebilic's underlying assumption makes no sense; the Office Action assumes that, were the NIH panelists to make their evaluations in Declaration form, their

opinions would somehow be transformed from 'novel, risky, and even outrageous' to the opposite, when evaluating Dr. Murphy's grant proposal for safety and efficacy.

(3) Mr. Prebilic's continued assertion, that the claim terms "permanently", "fixed", "invariable", and "continuously" are relative terms, is plainly preposterous. Mr. Prebilic points to no sources outside of this application which would support his position; the intrinsic evidence in this record, which has priority over any extrinsic evidence the Office Action could have included, plainly shows that Appellant's use of these terms in the claims excludes the interpretations the Office Action takes.

(4) Mr. Prebilic's assertion that the inclusion in *Flesler*'s device of electronics that control the voltage applied to a patient's tissue means that *Flesler* can unequivocally control the patient's body's reaction to that voltage, is again completely groundless. Furthermore, the fact that *Flesler*'s claims may have met the bare minimums of operability for patentable subject matter under 35 U.S.C. § 101, to wit, that they likely work a *de minimus* amount, does not mean that *Flesler*'s methods and devices can actually control blood flow. *Flesler* is only a published patent application, and therefore does not benefit from any presumption of operability or enablement.

(5) Appellant faults one of the prior Office Action's clear use of ***impermissible*** hindsight, that is, hindsight other than that that is intrinsic in the patentability inquiry; that Office Action presented no reasoning or additional facts in this record that weighs against this inescapable conclusion. *Flesler* and *Ruiz* are not "obviously" linked by someone of "ordinary" skill; indeed, there actually are not specialists who are experts in the separate arts of both disclosures, a combination that would truly demonstrate extraordinary skill. Combining *Ruiz* and *Flesler* in the manner alleged by Mr. Prebilic to be obvious is artificial and only possible after reading this patent application. The fact that millions of medical articles have been published without any of them alluding to the claimed combination speaks to that simple fact. It also speaks to the novelty and non-obviousness of the claimed combinations, which is clear in that context. To propose that the claimed combination is obvious to someone of "ordinary" skill is preposterous, because it would require extraordinary skill, and because there actually is no one

skilled in both of the applicable areas: placing vascular devices, and electrical stimulation of smooth muscle.

In the Response to Arguments of the Office Action, which begins at page 6 thereof, Mr. Prebilic again evinced a lack of appreciation of the obviousness inquiry, stating:

> In response to the traversal that the NIH panelists' skill levels are "higher than that of a routineer in these arts" . . . , the Examiner notes that they are not be [sic] qualified to determine obviousness under Section 103 because it requires one of ordinary skill. . . .

While Appellant believes that this statement speaks for itself, the statement plainly demonstrates that, throughout the prosecution of this application, Mr. Prebilic has applied an incorrect standard of patentability to the claimed subject matters. When persons of skill higher, than that of a person of ordinary skill in the art, are of the opinion that a medical method should not be performed, it is strong evidence that the method would not have been obvious to the less skilled person of ordinary skill.

Appellant respectfully submits that one of ordinary skill in the art, upon a full and fair reading of *Flesler* and *Ruiz*, would not be motivated to replace *Flesler*'s external (to the artery) and intermittent blood flow reduction methodology with an internal (to the artery), permanent blood flow restrictor, such as generally disclosed in *Ruiz*. *Flesler*, as discussed above, is singularly interested in only discontinuously and intermittently restricting the blood flow to the small intestine, timed to correspond to the presence of food in the small intestine; this is why *Flesler* suggests the placement of sensors in the body to detect food, and/or to configure the logic of the apparatus to permit its activation in synch with a meal. *Flesler* is also only concerned with modifying the blood flow to the small intestine by external stimulation of the artery that supplies blood to the small intestine, and not to an internal (to the artery) modification. Nowhere does *Ruiz* disclose or suggest that his stent should be used to treat obesity in a patient. *Yurek*'s disclosure adds nothing to this analysis.

Appellant respectfully submits, therefore, that a person of ordinary skill in the art, at the time of Appellant's invention, would not have looked to *Ruiz* for a stent to restrict blood flow for

Flesler's method. Because *Flesler* is only concerned with externally implemented, intermittent reduction in the blood flow to an artery, and *Ruiz*'s stent is a permanent, internal solution for treating pulmonary circulation overload, *Flesler* teaches directly away from the addition or substitution of *Ruiz*'s stent. Nowhere does *Flesler* indicate or suggest that permanent, internally-achieved blood flow reduction is desirable, and instructs the ordinarily skilled artisan that intermittent, externally achieved blood flow reduction (the opposite of that claimed) is how to treat obesity. *Ruiz* is, of course, completely ignorant of the possibility of using a reduction in blood flow to particular arteries to treat obesity, as it is singularly interested in treating pressure overload distal of the pulmonary artery, and therefore understandably fails to provide any motivation, suggestion, or guidance to use his stent in *Flesler*'s method.

Accordingly, Mr. Prebilic and the Office Action fail to make out a *prima facie* case of obviousness, including a rational reason related the claimed subject matter to make up for the deficiencies of the prior art with respect to the claimed combinations.

(b) Claim 14

The subject matter of Claim 14 is an example of how *Flesler* teaches away from the claimed combinations. Claim 14 relates to the method of Claim 10, and further requires adjusting the second portion of the endograft to achieve a pressure change within a desired range so that abdominal pain not related to meals does not occur. As well know to those of ordinary skill in the art, the reduction in the flow cross section in a fluid lumen throttles the flow, creating a pressure drop across the flow restriction with a corresponding decrease in the flow through the lumen.

Claim 14 is separately patentable from the subject matter of Claims 1 and 10, from which it depends. *Flesler* completely fails to identify non-meal related pain as a problem, because his method is entirely meal-oriented; in view of the several-fold increase in blood supply to the small intestine during meal digestion, and the fact that *Flesler*'s method does nothing to the blood supply at other times, *Flesler* (and the skilled artisan) would not expect the patient to

experience pain outside of mealtimes to begin with. There is nothing in *Flesler* or *Ruiz* to suggest that they would associate non-mealtime pain with the reduction in small intestine blood flow, or to suggest that alleviation of that pain could be achieved by changing the permanent, invariable blood flow restriction to the small intestines. Analysis of the subject matter of Claim 14, like those of the other pending claims, against *Flesler* and *Ruiz* further supports the patentability of Claim 1 *et sqq*.

Thus, assuming, *arguendo*, that a person of ordinary skill in the art would somehow find the subject matter of Claims 1 and 10 to not be patentable in view of *Flesler* and *Ruiz*, Mr. Prebilic has not identified any evidence in this record: that the additional subject matter of Claim 14, adjusting the second portion of the endograft to achieve a pressure change within a desired range so that abdominal pain not related to meals does not occur, is present in the prior art; or that a person of ordinary skill in the art would find a rational reason to make up for this deficiency in a hypothetical *Flesler/Ruiz* hybrid method to arrive at the combination claimed in Claim 14; or that there is some other reason why this deficiency in a hypothetical *Flesler/Ruiz* hybrid method would have otherwise been obvious to a person of ordinary skill in the art at the time of Appellant's invention.

(ii) Rejections under 35 U.S.C. § 102/103

(a) Claim 23, under section 102

Claim 23 is separately patentable from the other claims in this application. Claim 23 relates to a method of treating morbid obesity in a patient, comprising permanently reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient.

Mr. Prebilic alleges that several of the terms used in Claims 23-25 are identically met by *Flesler*, stating:

> The reduction is considered to be permanent, fixed, invariable, and continuous to the extent required because these terms are terms of relative degree. The Flesler device can and is used for permanent, fixed, invariable, and continuous way at least for a period of time.

(Office Action, page 4). Appellant strongly disagrees.

There is nothing relative about any of the accused terms. Appellant has used the particular terms in the claims in their normal English usage, and Mr. Prebilic's cavalier announcement that they are "terms of relative degree" is plainly wrong. It is truly incomprehensible how any of these terms are dependent on, and therefore relative to, any other parameter; certainly, Mr. Prebilic's inability to identify the other things upon which these terms could possible vary is a plain indication that, in fact, there are no such other variables. M.P.E.P. § 2173.05(b) discussed at great length what are the sorts of terms that are "terms of relative degree", and none of the terms used in the pending claims are of that ilk. M.P.E.P. § 2111.01 instructs the patent examining corps that "THE WORDS OF A CLAIM MUST BE GIVEN THEIR 'PLAIN MEANING' UNLESS SUCH MEANING IS INCONSISTENT WITH THE SPECIFICATION" (emphasis in original); the use of the claim terms is completely consistent with the use in the specification and are their 'plain meanings'. Mr. Prebilic's attempted lexicography is clearly an error, and the prior art plainly fails to disclose, describe, or fairly suggest methods for treating morbid obesity which involve permanent, fixed, invariable, and/or continuous reduction in the blood flow through blood vessels as recited in the pending claims.

Flesler describes intermittently electrically stimulating the tissues around the outside of a blood vessel to cause it to temporarily constrict, thus temporarily reducing the blood flow through that blood vessel. There is nothing whatsoever that is permanent about the blood flow reduction that *Flesler* proposes: it is entirely transient. Indeed, *Flesler* discussed terminating the therapy at the patient's discretion, or at non-meal times, plainly making *Flesler*'s method non-permanent. Accordingly, the rejection of Claim 23 under section 102(b) is reversible error.

(b) Claim 23, under section 103

Mr. Prebilic alternatively argues that the term "permanent" in Claim 23 may not read on *Flesler*'s method. In order to combat this deficiency with respect to the subject matter of Claim 23, Mr. Prebilic turns to *Ruiz*. Mr. Preblic alleges:

> Ruiz teaches that it was known to the artery treatment art to make blood flow reduction more permanent, fixed, invariable, and continuous; see the previously cited portions thereof. Therefore, it is the examiner's position that it would have been obvious to utilize the Ruiz device in addition to the Flesler device to provide a set degree of minimal constriction that can be varied with the electrical stimulation means or for the same reasons that Ruiz utilizes the same.

Thus, Mr. Prebilic appears to now advocate a compound therapy for the treatment of obesity: install a *Ruiz*-type device inside the applicable artery, coupled with the application of intermittent electrical stimulation to the outside of that same artery. Appellant vigorously traverses this rejection.

As a first matter, as discussed above, there is overwhelming objective evidence in this record that the methods described and claimed herein are non-obvious, which applies with equal force to the subject matter of Claim 23.

Mr. Prebilic's proposed combined therapy would not lead to further reductions in blood flow, and would therefore not be an obvious combination. Installation of a *Ruiz*-type stent in a blood vessel identified in *Flesler* would likely reduce blood flow through that vessel. Application of *Flesler*'s intermittent electrical stimulation upstream or downstream of the implantation site of the *Ruiz*-type stent, causing temporary constriction of the blood vessel at that location, would not create additional blood flow restriction, because the larger of the two blood flow constrictions (*Ruiz*'s stent, or *Flesler*'s electrically-induced contraction) would dictate the flow rate; the constrictions are not additive, as is a well-known fact from college level fluid mechanics. If the sites are the same, that is, if the *Flesler* electro-stimulation were to be applied at the location of the *Ruiz*-type stent, the blood vessel would merely constrict around the stent,

but there is absolutely no evidence in this record that the blood vessel would further reduce the cross sectional area of the stent at its smallest internal diameter 13; indeed, it would, at best, reduce the internal diameter of the larger end portions, which would not further reduce blood flow, as described above. Thus, a person of ordinary skill in the art, were they to have some rational reason for looking at *Flesler* and *Ruiz* for the treatment of obesity, would immediately understand that combining them in the manner alleged by Mr. Prebilic to be obvious, would have no therapeutic effect beyond that of either one of them.

Furthermore, as previously argued with respect to the subject matter of Claim 1 *et sqq.*, there is no rational reason, related to the subject matters of *Flesler* and *Ruiz*, to replace the highly intermittent, temporary, external-to-the-blood-vessel process described in *Flesler* with the intra-luminal vessel implantation of a stent, described in *Ruiz*. *Flesler* and *Ruiz* relate to entirely different subject matters and disease states, and approach their respective subject matters from entirely different ways. Mr. Prebilic identifies no evidence in the record that substantiates his claim that a person of ordinary skill in the art would want to make *Flesler*'s blood flow restriction more permanent, or that a person of ordinary skill in the art would want to use *Ruiz*'s stent to restrict blood flow in an artery other than the pulmonary artery, much less one that supplies blood as recited in Claim 23 for any purpose.

For at least the forgoing reasons, Appellant respectfully submits that a *prima facie* case of obviousness has not been made out with respect to the subject matter of Claim 23. Accordingly, the rejection of Claim 23 under section 103(a) is reversible error.

(c) Claim 24, under section 102

Claim 24 is separately patentable from the other claims in this application. Claim 24 relates to a method of treating morbid obesity in a patient, comprising reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, a fixed, invariable amount in the patient.

Mr. Prebilic alleges that several of the terms used in Claims 23-25 are identically met by *Flesler*, stating:

> The reduction is considered to be permanent, fixed, invariable, and continuous to the extent required because these terms are terms of relative degree. The Flesler device can and is used for permanent, fixed, invariable, and continuous way at least for a period of time.

(Office Action, page 4). Appellant strongly disagrees.

There is nothing relative about any of the accused terms. Appellant has used the particular terms in the claims in their normal English usage, and Mr. Prebilic's cavalier announcement that they are "terms of relative degree" is plainly wrong. It is truly incomprehensible how any of these terms are dependent on, and therefore relative to, any other parameter; certainly, Mr. Prebilic's inability to identify the other things upon which these terms could possible vary is a plain indication that, in fact, there are no such other variables. M.P.E.P. § 2173.05(b) discussed at great length what are the sorts of terms that are "terms of relative degree", and none of the terms used in the pending claims are of that ilk. M.P.E.P. § 2111.01 instructs the patent examining corps that "THE WORDS OF A CLAIM MUST BE GIVEN THEIR 'PLAIN MEANING' UNLESS SUCH MEANING IS INCONSISTENT WITH THE SPECIFICATION" (emphasis in original); the use of the claim terms is completely consistent with the use in the specification and are their 'plain meanings'. Mr. Prebilic's attempted lexicography is clearly an error, and the prior art plainly fails to disclose, describe, or fairly suggest methods for treating morbid obesity which involve permanent, fixed, invariable, and/or continuous reduction in the blood flow through blood vessels as recited in the pending claims.

Flesler describes intermittently electrically stimulating the tissues around the outside of a blood vessel to cause it to temporarily constrict, thus variably reducing the blood flow through that blood vessel. There is nothing whatsoever that is fixed or invariable about the blood flow reduction that *Flesler* proposes: it is entirely variable, as *Flesler* wants it to be. Indeed, *Flesler*'s

variation of the duty cycle of his plainly makes *Flesler*'s method variable. Accordingly, the rejection of Claim 24 under section 102(b) is reversible error.

(d) Claim 24, under section 103

Mr. Prebilic alternatively argues that the term "fixed, invariable" in Claim 23 may not read on *Flesler*'s method. In order to combat this deficiency with respect to the subject matter of Claim 23, Mr. Prebilic turns to *Ruiz*. Mr. Preblic alleges:

> Ruiz teaches that it was known to the artery treatment art to make blood flow reduction more permanent, fixed, invariable, and continuous; see the previously cited portions thereof. Therefore, it is the examiner's position that it would have been obvious to utilize the Ruiz device in addition to the Flesler device to provide a set degree of minimal constriction that can be varied with the electrical stimulation means or for the same reasons that Ruiz utilizes the same.

Thus, Mr. Prebilic appears to now advocate a compound therapy for the treatment of obesity: install a *Ruiz*-type device inside the applicable artery, coupled with the application of intermittent electrical stimulation to the outside of that same artery. Appellant vigorously traverses this rejection.

As a first matter, as discussed above, there is overwhelming objective evidence in this record that the methods described and claimed herein are non-obvious, which applies with equal force to the subject matter of Claim 24.

Mr. Prebilic's proposed combined therapy would not lead to further reductions in blood flow, and would therefore not be an obvious combination. Installation of a *Ruiz*-type stent in a blood vessel identified in *Flesler* would likely reduce blood flow through that vessel. Application of *Flesler*'s intermittent electrical stimulation upstream or downstream of the implantation site of the *Ruiz*-type stent, causing temporary constriction of the blood vessel at that location, would not create additional blood flow restriction, because the larger of the two blood flow constrictions (*Ruiz*'s stent, or *Flesler*'s electrically-induced contraction) would dictate the

flow rate; the constrictions are not additive, as is a well-known fact from college level fluid mechanics. If the sites are the same, that is, if the *Flesler* electro-stimulation were to be applied at the location of the *Ruiz*-type stent, the blood vessel would merely constrict around the stent, but there is absolutely no evidence in this record that the blood vessel would further reduce the cross sectional area of the stent at its smallest internal diameter 13; indeed, it would, at best, reduce the internal diameter of the larger end portions 11, 12, which would not further reduce blood flow, as described above. Thus, a person of ordinary skill in the art, were they to have some rational reason for looking at *Flesler* and *Ruiz* for the treatment of obesity, would immediately understand that combining them in the manner alleged by Mr. Prebilic to be obvious, would have no therapeutic effect beyond that of either one of them.

Furthermore, as previously argued with respect to the subject matter of Claim 1 *et sqq.*, there is no rational reason, related to the subject matters of *Flesler* and *Ruiz*, to replace the highly intermittent, temporary, external-to-the-blood-vessel process described in *Flesler* with the intra-luminal vessel implantation of a stent, described in *Ruiz*. *Flesler* and *Ruiz* relate to entirely different subject matters and disease states, and approach their respective subject matters from entirely different ways. Mr. Prebilic identifies no evidence in the record that substantiates his claim that a person of ordinary skill in the art would want to make *Flesler*'s blood flow restriction more fixed and invariable, or that a person of ordinary skill in the art would want to use *Ruiz*'s stent to restrict blood flow in an artery other than the pulmonary artery, much less one that supplies blood as recited in Claim 24 for any purpose.

For at least the forgoing reasons, Appellant respectfully submits that a *prima facie* case of obviousness has not been made out with respect to the subject matter of Claim 24. Accordingly, the rejection of Claim 24 under section 103(a) is reversible error.

(e) Claim 25, under section 102

Claim 25 is separately patentable from the other claims in this application. Claim 25 relates to a method of treating morbid obesity in a patient, comprising continuously reducing

gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient for a time effective to reduce the patient's weight.

Mr. Prebilic alleges that several of the terms used in Claims 23-25 are identically met by *Flesler*, stating:

> The reduction is considered to be permanent, fixed, invariable, and continuous to the extent required because these terms are terms of relative degree. The Flesler device can and is used for permanent, fixed, invariable, and continuous way at least for a period of time.

(Office Action, page 4). Appellant strongly disagrees.

There is nothing relative about any of the accused terms. Appellant has used the particular terms in the claims in their normal English usage, and Mr. Prebilic's cavalier announcement that they are "terms of relative degree" is plainly wrong. It is truly incomprehensible how any of these terms are dependent on, and therefore relative to, any other parameter; certainly, Mr. Prebilic's inability to identify the other things upon which these terms could possible vary is a plain indication that, in fact, there are no such other variables. M.P.E.P. § 2173.05(b) discussed at great length what are the sorts of terms that are "terms of relative degree", and none of the terms used in the pending claims are of that ilk. M.P.E.P. § 2111.01 instructs the patent examining corps that "THE WORDS OF A CLAIM MUST BE GIVEN THEIR 'PLAIN MEANING' UNLESS SUCH MEANING IS INCONSISTENT WITH THE SPECIFICATION" (emphasis in original); the use of the claim terms is completely consistent with the use in the specification and are their 'plain meanings'. Mr. Prebilic's attempted lexicography is clearly an error, and the prior art plainly fails to disclose, describe, or fairly suggest methods for treating morbid obesity which involve permanent, fixed, invariable, and/or continuous reduction in the blood flow through blood vessels as recited in the pending claims.

Flesler describes intermittently electrically stimulating the tissues around the outside of a blood vessel to cause it to temporarily constrict, thus temporarily reducing the blood flow through that blood vessel. There is nothing whatsoever that is continuous about the blood flow

reduction that *Flesler* proposes: it is entirely transient. The electrical pulses applied during *Flesler*'s process results in pulsatile constrictions of the target blood vessel, as plainly illustrated in *Flesler*'s Fig. 3A. Accordingly, the rejection of Claim 25 under section 102(b) is reversible error.

(f) Claim 25, under section 103

Mr. Prebilic alternatively argues that the term "continuous" in Claim 25 may not read on *Flesler*'s method. In order to combat this deficiency with respect to the subject matter of Claim 25, Mr. Prebilic turns to *Ruiz*. Mr. Preblic alleges:

> Ruiz teaches that it was known to the artery treatment art to make blood flow reduction more permanent, fixed, invariable, and continuous; see the previously cited portions thereof. Therefore, it is the examiner's position that it would have been obvious to utilize the Ruiz device in addition to the Flesler device to provide a set degree of minimal constriction that can be varied with the electrical stimulation means or for the same reasons that Ruiz utilizes the same.

Thus, Mr. Prebilic appears to now advocate a compound therapy for the treatment of obesity: install a *Ruiz*-type device inside the applicable artery, coupled with the application of intermittent electrical stimulation to the outside of that same artery. Appellant vigorously traverses this rejection.

As a first matter, as discussed above, there is overwhelming objective evidence in this record that the methods described and claimed herein are non-obvious, which applies with equal force to the subject matter of Claim 25.

Mr. Prebilic's proposed combined therapy would not lead to further reductions in blood flow, and would therefore not be an obvious combination. Installation of a *Ruiz*-type stent in a blood vessel identified in *Flesler* would likely reduce blood flow through that vessel. Application of *Flesler*'s intermittent electrical stimulation upstream or downstream of the implantation site of the *Ruiz*-type stent, causing temporary constriction of the blood vessel at that

location, would not create additional blood flow restriction, because the larger of the two blood flow constrictions (*Ruiz*'s stent, or *Flesler*'s electrically-induced contraction) would dictate the flow rate; the constrictions are not additive, as is a well-known fact from college level fluid mechanics. If the sites are the same, that is, if the *Flesler* electro-stimulation were to be applied at the location of the *Ruiz*-type stent, the blood vessel would merely constrict around the stent, but there is absolutely no evidence in this record that the blood vessel would further reduce the cross sectional area of the stent at its smallest internal diameter 13; indeed, it would, at best, reduce the internal diameter of the larger end portions, which would not further reduce blood flow, as described above. Thus, a person of ordinary skill in the art, were they to have some rational reason for looking at *Flesler* and *Ruiz* for the treatment of obesity, would immediately understand that combining them in the manner alleged by Mr. Prebilic to be obvious, would have no therapeutic effect beyond that of either one of them.

Furthermore, as previously argued with respect to the subject matter of Claim 1 *et sqq.*, there is no rational reason, related to the subject matters of *Flesler* and *Ruiz*, to replace the highly intermittent, temporary, external-to-the-blood-vessel process described in *Flesler* with the intra-luminal vessel implantation of a stent, described in *Ruiz*. *Flesler* and *Ruiz* relate to entirely different subject matters and disease states, and approach their respective subject matters from entirely different ways. Mr. Prebilic identifies no evidence in the record that substantiates his claim that a person of ordinary skill in the art would want to make *Flesler*'s blood flow restriction more continuous, or that a person of ordinary skill in the art would want to use *Ruiz*'s stent to restrict blood flow in an artery other than the pulmonary artery, much less one that supplies blood as recited in Claim 25 for any purpose.

For at least the forgoing reasons, Appellant respectfully submits that a *prima facie* case of obviousness has not been made out with respect to the subject matter of Claim 25. Accordingly, the rejection of Claim 25 under section 103(a) is reversible error.

VIII. CONCLUSION

For at least the foregoing reasons, Appellant respectfully submits that the rejections of the claims in this patent application are in error, and therefore respectfully requests reversal thereof.

Respectfully submitted,

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Date: 18 November 2008

CLAIMS APPENDIX

1. A method of treating morbid obesity in a patient comprising:

reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient, including placing a blood flow reducing device inside an artery that carries blood to the small intestine.

3. A method in accordance with Claim 1, wherein placing comprises placing the blood flow reducing device inside an artery selected from the group consisting of the superior mesenteric artery, the inferior mesenteric artery, and both.

4. A method in accordance with Claim 3, wherein the blood flow reducing device comprises an endograft positioned inside the artery.

5. A method in accordance with Claim 1, wherein said artery that carries blood to the small intestine is the gastroduodenal artery.

6. A method in accordance with Claim 5, wherein the blood flow reducing device comprises an endograft positioned inside the artery.

8. A method in accordance with Claim 1, wherein said artery that carries blood to the small intestine is the superior mesenteric artery.

9. A method in accordance with Claim 8, wherein the blood flow reducing device comprises an endograft positioned inside the artery.

10. A method in accordance with Claim 1, wherein placing comprises placing an endograft inside the artery, the endograft including a first portion having a size selected to hold the

endograft in place in the artery, and a second portion smaller than the first portion that reduces blood flow through the artery.

11. A method in accordance with Claim 10, further comprising:
moving a sleeve surrounding the endograft through the artery; and
wherein placing comprises deploying the endograft from within the sleeve into the artery.

12. A method in accordance with Claim 10, further comprising:
expanding the second portion of the endograft to increase the blood flow rate through the artery.

13. A method in accordance with Claim 10, wherein said second portion includes a swellable material.

14. A method in accordance with Claim 10, further comprising:
adjusting the second portion of the endograft to achieve a pressure change within a desired range so that abdominal pain not related to meals does not occur.

23. A method of treating morbid obesity in a patient comprising:
permanently reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient.

24. A method of treating morbid obesity in a patient comprising:
reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, a fixed, invariable amount in the patient.

25. A method of treating morbid obesity in a patient comprising:

continuously reducing gastric blood flow, duodenal blood flow, mesenteric blood flow, jejunal blood flow, ileal blood flow, or combinations thereof, in the patient for a time effective to reduce the patient's weight.

EVIDENCE APPENDIX

Additional evidence is cited in this Brief, as follows:

(1) Two NIH grant proposals;

(2) NIH panel responses to the two NIH grant proposals of item (1); and

(3) Resumes and/or *curriculum vitae* of NIH panel participants responsible for the responses of item (2).

Items (1) and (2) were filed after a final rejection of the claims in an Office Action mailed 15 June 2007, and were entered into the record after the filing of a Request for Continued Examination ("RCE") and the subsequent issuance of an Office Action on 22 August 2007. Item (3) was filed on 7 April 2008 with an RCE, and was entered into the record by the issuance of an Office Action on 30 July 2008.

Research Design and Methods

This investigation involves two "phases", development of the device prototype and testing in an animal model. These "phases" will be conducted concurrently and not in sequence. The process will be iterative and heuristic. That is, a number of prototypes will be developed until benchtop performance tests demonstrate the ability to fully expand the ends of the stent while the center portion remains undilated or minimally expanded. Once this is satisfied, the stent prototype will be coated with PTFE and its implantation attempted, with a complete angiographic and hemodynamic evaluation. The next prototype will be modified to adapt to any shortcomings with the first one. We have estimated that we need 18 evaluable study animals to detect differences in treatment effect between the two proposed treatment groups, and have included two extra in consideration that the first prototype may not be perfect, as well as for other potential drop out. We estimate that we may develop up to a half dozen stents for benchtop testing.

Proprietary Prototype Development

The prototype stents will be produced by direct ultraviolet (UV) ablation of portions of hollow 316 stainless steel tubing. The first stents we produce will be made using the design parameters we developed in the preliminary studies. Figure 5 is an illustration of the expanded stent elements. The center portion of the stent will be more ridged because the struts will be wider and they will have thicker shoulders. We will test the expansion of these stents by expanding them with a conventional balloon catheter and measuring the expanded diameter of the stent at eleven locations along the length of the stent. This will be done at 25%, 50%, 75%, 100% and 125% of the designed expansion pressures. We will be looking for uniform and symmetric expansion of the stent, indications of any damage to the expansion balloon, problems with balloon deflation, and problems with balloon extraction. These experiments will be done with the catheter in free air and with the catheter in a simulated pig artery. It is expected that these initial studies will provide technical data which will assist in the next iteration of the stent design. As in conventional stent production, post processing operations may be required to address specific problems such as sharp edges on the struts. The ablation method of stent production will have a much smaller effect on the metallurgy of the stent and we do not expect any post processing will be required to remove slag.

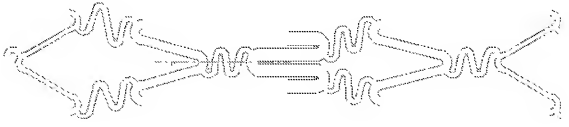

Figure 5. Illustration of expanded stent elements

The controlled ablation metal removal will allow some design freedom not available when using other production methods. One example of this is we can remove a portion of the wall material at the ends of the stent so that the ends will expand with a lower balloon pressure than the middle portion of the stent. Many conventional stents are built with struts having a square crossection (i.e. the width and thickness of the strut are nominally equal). In our first design we will reduce the width of the strut as we go from the middle of the stent to the ends. We expect that information from the testing of those stents will indicate how much thinner the struts will have to be made to meet the design requirements of an expanded diameter of 7mm at the ends and 2mm at the center. It is our goal to design the stent so that the desired lumen diameter on deployment can be achieved with a single balloon design. The test procedure for the

initial design will be updated to assure testing is complete and then the redesigned stents will be produced and tested.

Once the prototype stent framework has been developed, a "skin" will be applied to improve the ability to achieve a pressure gradient across the prosthesis, to reduce turbulence in the lumen and between the lumen and artery wall, and to reduce the likelihood of mural thrombus forming and embolizing downstream into bowel arteries. The "skin" will be expanded polytetrafluoroethylene (ePTFE), which is ideal for this application as it can be bonded securely by a proprietary patented process developed by Atrium Medical (Hudson, NH) while being low in bulk and preserving many of the advantages of a low-profile system. These include small access hole and trackability/deliverability to the artery of interest. The PTFE encapsulation is completed by taking a small ePTFE tube typically 1 mm in diameter and a little longer than twice the length of the stent. This tube is placed within the stent, with half of the excess length of material extending from either edge of the stent. Then the additional length of material is rolled over the outer edge of the stent to cover the outside of the stent. The outer layer is overlapped in this process. Once the PTFE is overlapped it is then sintered where the PTFE material binds together to form one piece. A quote for coating 10 stents with ePTFE is included from Atrium Medical. After coating the stents with PTFE, they will be gas-sterilized. The coated stents will be retested by the above procedures to assure design parameters can be met with the coated stents and to assure the coating remains intact through the stent expansion process.

Prototype Testing: Animal Experiment

The animal experiment will be conducted in an 11,000 square foot animal facility at Rhode Island Hospital (Providence, RI) including an operating room, angiographic and fluoroscopic imaging equipment. The protocol will be submitted to the Rhode Island Hospital Animal Care and Use Committee, and Dr. Murphy will be the principal investigator. A collaboration letter from Luis Sousa, Ph.D., director of the animal laboratory at Rhode Island Hospital, is included in this application. All animal care will be provided per Rhode Island Hospital standard operating procedures and policy which are accordance with the U.S.D.A Animal Welfare Act Regualtions done according to the ILAR *Guide for Care and Use of LaboratoryAnimals*. The animal facility has Full-Accreditation with the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC-International).

Once the reducing stent-graft prosthesis is developed, the experiment in swine will be conducted. Prior to randomization, stent placements will be attempted in adult farm swine. When a suitable stent-graft is developed, the survival experiment may be conducted in smaller animals, such as Yucatan or Hanford minipigs, if placement in their smaller arteries is deemed feasible at the time. Swine are an excellent model of obesity[23] and will gain about a pound a day when fed liberally. They are also large enough to be treated with the prosthesis, in contrast to smaller animal models. Pig mesenteric arterial anatomy is similar to humans and has been well-characterized angiographically and pathologically[5]. In the pig, a celiac, "cranial" mesenteric artery, and "caudal" mesenteric arise from the abdominal aorta, with the "cranial" mesenteric artery supplying most of the small intestine to the ascending colon[5].

Pigs will be observed for dietary intake for 3 days prior to the procedure by weighing all dispensed food and subtracting that not consumed, and pigs will also be weighed pre-procedure. On the day of the procedure, animals will receive a dose of 325 mg aspirin orally, and then anesthesia will be induced with Telazol (tiletamine hydrochloride 50 mg/mL, zolazepam hydrochloride 50 mg/mL) 6 mg/kg and Rompum (23 mg/mL, (xylazine hydrochloride) by intramuscular (IM) injection and sodium pentothal to effect (20mg/kg) intravenously (IV), and then maintained under isoflurane gas anesthesia. Preoperatively, the animals also will be given Atropine 0.05 mg/kg, and buprenorophine (0.01 mg/kg intramuscularly (IM)) for pain. They will be placed supine in a sterile operating room environment, and the skin disinfected first clipping the hair around the surgical area in both groin regions followed with alternating scrubs with

providone-iodine scrub and alcohol, and then with povidone-iodine solution. Access to one or both femoral arteries will be performed by cut down after assurance of adequate anesthesia. Once the common femoral arterie(s) are dissected free, vessel loops will be placed proximally and distally. Puncture of the common femoral artery(ies) will be done using an 18 G or 19G hollow-core needle, and a guide wire placed under fluoroscopic guidance into the upper abdominal aorta. A vascular sheath will be placed and connected to a flush of half normal saline at an infusion rate of 15-30 milliliters/hour. A flush catheter will be placed through the sheath and a flush abdominal aortogram obtained to map out the blood supply to the intestine. Selective catheterization of the gastroduodenal artery and superior ("cranial") mesenteric artery will be done with a shaped catheter and arteriography done of those circulations.

Randomization to sham procedure or stent-graft placement will be done after diagnostic arteriography using an envelope system. For sham treatment group animals, the catheters will then be removed and wounds closed using standard techniques. For active treatment group animals, occlusion of the gastroduodenal artery will be done proximally with coils placed transcatheter. The endovascular prosthesis will be placed in the superior ("cranial") mesenteric artery and deployed. The endoprosthesis is designed to inflate like a dumbbell, narrow in the middle but wide at its ends. The approximate lumen diameter on deployment will be 2 mm in the middle and 6 or 7 at the ends. Pressure measurements will be done distal and proximal to the prosthesis before and after injection of 25 mg of the alpha blocker tolazoline into the SMA. Tolazoline is a vasodilator and will augment any pressure gradient, or bring out a pressure gradient where none existed in the resting state. The endograft lumen diameter will then be increased using angioplasty balloons if needed so that there is no or minimal gradient at rest (less than 10 mm Hg mean). Final pressure gradients at rest and after tolazoline will be recorded. Subsequently, wounds will be closed using absorbable sutures beneath the skin (2-0 through 4-0 Vicryl, Ethicon/Johnson&Johnson, Warren, NJ) and staples for the skin, and animals will then emerge from anesthesia.

The animals will be monitored for two hours post-op to monitor behavior and level of activity to make sure that the animals have completely recovered from anesthesia. They will be evaluated q 12 hours and given analgesia, buprenorphine 0.01mg/kg IM for 24 hrs for pain. They will receive aspirin 325 mg orally each day for platelet inhibition, anticoagulation is not done in clinical practice for humans with stents grafts and won't be done. The pigs will be closely monitored for 7 days for changes in activity, behavior, eating and watering habits. If the pig is found to not be eating or to be experiencing any discomfort, the veterinarian will be consulted and additional doses of Buprenorphine may be administered at their discretion. Euthanasia will be performed in an instance were the animal is found to be in significant distress or discomfort, continuing decreased food/water intake, or exibiting lethargy despite treatment at the discretion of the veterinarian in consultation with the investigators.

Thereafter, the animals will be checked daily for any changes in activity, behavior, eating habits, urine or feces output. If any change is noted, appropriate evaluation will be done to determine if the animal is experiencing any pain or if there is an infection present (infection will be evaluated by visual examination of surgical sites for abnormal changes as well as temperature evaluation). They will be monitored for dietary caloric intake for 3 day periods at one week and one month post-procedure. Weighers will be trained on the laboratory standard method of weighing, including weighing on a consistent time of day, and will be blinded to the treatment group. After 60 days, pigs will be weighed and sacrificed. Gross inspection of the bowel and mesenteric artery endoprosthesis done for descriptive purposes, including the presence of bowel ischemia, stricture, infarction, intraarterial thrombus or intimal hyperplasia.

Statistical Analysis:

Data will be collected in laboratory notebooks and entered into a computer database (Access 2000, Microsoft, Redmond, WA) designed for this project. Data will be analyzed using StatView v.5.0.1 statistical software (SAS Institute, Cary, NC).

Primary endpoint:
Change in weight will be compared between treatment groups using repeated measures ANOVA with Group as a fixed effect. Sample size was estimated based on the anticipated difference between groups at 60 days (t-test). It is anticipated that the use of repeated measures ANOVA at analysis will be more sensitive and so the calculated sample size represents a conservative estimate of that required. The following assumptions are made:

- The mean weight for the population of pigs at baseline is 160 lbs
- After one month of ad lib feeding, the control group mean weight will be 170 lbs
- After one month of ad lib feeding, the treatment group mean weight will be 150 lbs
- The group standard deviation is 12 lbs
- The effect size, or standardized difference, ={(170-150)/12}=1.67

H_o: $\mu_{SH} = \mu_{ST}$
H_a: $\mu_{SH} \neq \mu_{ST}$

Where μ_{ST} is the primary endpoint estimate for the reducing stent-graft group and μ_{SH} is the primary endpoint estimate for the sham group at 60 days. Rejection of the null hypothesis will signify that the weight change between the two groups is significantly different. Given the above, with an α of .05 and power of 90%, a sample size of 18 (9 per group) evaluable subjects is needed (EaST 2000 software, Cytel Corporation, Cambridge, MA). We have inflated the sample size by two to account for study subject drop out such as for example due to technical failure of stent-graft implantation procedure and complications of either treatment, or drop out due to other unanticipated causes.

Secondary endpoints:
1. Estimate of dietary caloric intake—Pigs will be fed *ad lib*, and excess amounts of feed will be left in the pen with each pig. Caloric intake will be calculated by measuring standard feed prior to filling the feed dispensing bin, and then at the end of a three day period measuring how much is left in the bin and in the pen, and therefore how much was consumed. Caloric equivalents will be calculated according to the feed manufacturer's information. The change in average caloric intake over the 3 day period pre-intervention compared with one week and one month later will be compared using a t-test.
2. Adverse events—Adverse events like death, bowel infarction, diarrhea, aversion to food, infection, and reduced activity (water intake, bladder and bowel function) will be recorded and reported so that risks of the proposed can be understood, and any benefits in terms of weight loss be understood in the context of the challenges posed by these events

Key Personnel
Dr. Timothy Murphy is the Director of Quequechan Engineering, Inc., and an interventional radiologists practicing in Providence, Rhode Island. He is the Director of the Vascular Disease Research Center at Rhode Island Hospital, and a Professor, Research Track, of Diagnostic Imaging at Brown Medical School. He has over 13 years of experience as an interventional radiologist and performs procedures similar to those proposed as part of this experiment on a regular basis. He is a fellow of the Society of Interventional Radiology, the American Heart Association, the Society of Vascular Medicine and Biology, and the American College of Radiology. He is the principal investigator of the CLEVER multicenter

randomized clinical trial (Claudication: Exercise Vs. Endoluminal Revascularization, NHLBI R01 HL077221), and co-principal investigator of the CORAL Study (Cardiovascular Outcomes with Renal Atherosclerotic Lesions, NHLBI R01 HL071556-01). In addition to participating in prototype design and development, Dr. Murphy will perform the animal experiment as principal investigator, will collect and analyze data, and report study results.

Dr. Lamar Bullock received a Ph.D. in physics from Michigan State University and is an Adjunct Professor of Physics at University of Massachusetts-Dartmouth, and is the director of the photonics laboratory that includes the IX-300 Micro-Machining Laser. Dr. Bullock was formerly president of Boston Laser Technology, where he developed a unique excimer laser-based manufacturing process. He also designed and built laser imaging equipment to apply this process to volume manufacturing of a coronary stent for a company, Buckbee-Mears (St. Paul, MN), that was developing stents for Cordis/Johnson&Johnson (Warren, NJ), one of the largest manufacturers of vascular stents in the world. This project required close coordination with the stent designers to make optimal use of a new laser-based manufacturing process.

Cong Wang is a graduate student in Physics at the University of Massachusetts-Dartmouth. He received his bachelor's degree with a major in Applied Chemistry, Beijing University of Technology in 2004, and has done research in the Institute of Physics, Chinese Academy of Science, on non-materials and superconductivity. As an intern at the University of Massachusetts Advanced Technology and Manufacturing Center, Cong Wang has acquired skills in the operation of the Excimer Laser Micro-Machining Center and CAD design of stents.

D. Research Design and Methods

This investigation involves two phases, development of the device prototype and testing in an animal model. These phases will be conducted concurrently and not in sequence as much as possible. That is, the process will be iterative and heuristic. A number of prototypes will be developed until bench top performance tests demonstrate the ability to fully expand the ends of the stent while the center portion remains undilated or minimally expanded. Once this is satisfied, the stent prototype will be coated with PTFE and its implantation attempted, with a complete angiographic and hemodynamic evaluation. The next prototype will be modified to adapt to any shortcomings with the first one. We have estimated (see section D.3, "Sample Size Estimate") that we need 18 evaluable study animals to detect differences in treatment effect between the two proposed treatment groups, and have included two extra in consideration that the first prototype may not be perfect, as well as for other potential drop out. We estimate that we may develop up to a half dozen stents for benchtop testing.

D. 1 Technology Development Plan

There is no commercially available medical device, stent or stent-graft, that assumes a variable-diameter shape (personal communication, Dorothy Abel in the Office of Device Evaluation at the FDA (301) 443-8517; dorothy.abel@fda.hhs.gov), and there is nothing available that would be remotely suitable for the proposed application. The devices will be made relatively inexpensively.

Developing a stent-graft that will inflate asymmetrically will be an engineering challenge. Commercially available balloon-expandable stent-grafts are designed to inflate symmetrically, with little diameter difference between the central and end portions during inflation. To do this, the dilatation balloon length is used similar to the device length. If the balloon is considerably longer than the stent-graft, it tends to inflate the "shoulders" of the balloon (or the part of the balloon not covered by the device) first, then the ends of the stent-graft, and finally the middle of the stent-graft. This can result in separation of the graft or fabric, and "accordioning" of the graft material into the center of the stent. This is highly undesirable. In order to engineer a stent-graft to intentionally dilate at its ends while maintaing relative constriction of the middle, the balloon should ideally be sized appropriately for the stent, but the stent will need more resistance to inflation in its center compared with the ends. Finally, bonding of the graft or fabric to the stent framework will have to be strong.

The prototype stents will be produced by direct ultraviolet (UV) ablation of portions of hollow 316 stainless steel tubing. The first stents we produce will be made using the design parameters we developed in the preliminary studies. Figure 5 is an illustration of the expanded stent elements. The center portion of the stent will be more ridged because the struts will be wider and they will have thicker shoulders. We will test the expansion of these stents by expanding them with a conventional balloon catheter and measuring the expanded diameter of the stent at eleven locations along the length of the stent. This will be done at 25%, 50%, 75%, 100% and 125% of the designed expansion pressures. We will be looking for uniform and smooth expansion of the stent, indications of any damage to the expansion balloon, problems with balloon deflation, and problems with balloon extraction. These experiments will be done with the catheter in free air and with the catheter in a simulated pig artery. It is expected that these initial studies will provide technical data which will assist in the next iteration of the stent design. As in conventional stent production, post processing operations may be required to address specific problems such as sharp edges on the struts. The ablation method of stent production will have a much smaller effect on the metallurgy of the stent and we do not expect any post processing will be required to remove slag.

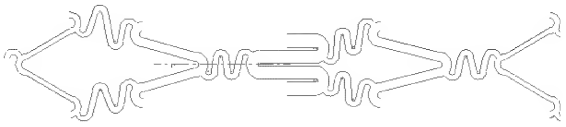

Figure 5. Illustration of expanded stent elements

The controlled ablation metal removal will allow some design freedom not available when using other production methods. One example of this is we can remove a portion of the wall material at the ends of the stent so that the ends will expand with a lower balloon pressure than the middle portion of the stent. Many conventional stents are built with struts having a square cross section (i.e. the width and thickness of the strut are nominally equal). In our first design we will reduce the width of the strut as we go from the middle of the stent to the ends. We expect that information from the testing of those stents will indicate how much thinner the struts will have to be made to meet the design requirements of an expanded diameter of 7mm at the ends and 2 mm at the center. It is our goal to design the stent so that the desired lumen diameter on deployment can be achieved with a single balloon design. The test procedure for the initial design will be updated to assure testing is complete and then the redesigned stents will be produced and tested.

Once the prototype stent framework has been developed, a "skin" will be applied to improve the ability to achieve a pressure gradient across the prosthesis, to reduce turbulence in the lumen and between the lumen and artery wall, and to reduce the likelihood of mural thrombus forming and embolizing downstream into bowel arteries. The "skin" will be expanded polytetrafluoroethylene (ePTFE), which is ideal for this application as it can be bonded securely by a proprietary patented process developed by Atrium Medical (Hudson, NH) while being low in bulk and preserving many of the advantages of a low-profile system. These include small access hole and trackability/deliverability to the artery of interest. The PTFE encapsulation is completed by taking a small ePTFE tube typically 1 mm in diameter and a little longer than twice the length of the stent. This tube is placed within the stent, with half of the excess length of material extending from either edge of the stent. Then the additional length of material is rolled over the outer edge of the stent to cover the outside of the stent. The outer layer is overlapped in this process. Once the PTFE is overlapped it is then sintered where the PTFE material binds together to form one piece. This process results in a bond that is very strong. A quote for coating 10 stents with ePTFE is included from Atrium Medical. After coating the stents with PTFE, they will be gas-sterilized. The coated stents will be retested by the above procedures to assure design parameters can be met with the coated stents and to assure the coating remains intact through the stent expansion process.

D.2 Prototype Testing: Animal Experiment

The animal experiment will be conducted in an 11,000 square foot animal facility at Rhode Island Hospital (Providence, RI) including an operating room, angiographic and fluoroscopic imaging equipment. The protocol will be submitted to the Rhode Island Hospital Animal Care and Use Committee, and Dr. Murphy will be the principal investigator. A collaboration letter from Luis Sousa, Ph.D., director of the animal laboratory at Rhode Island Hospital, is included in this application. All animal care will be provided per Rhode Island Hospital standard operating procedures and policy which are accordance with the U.S.D.A Animal Welfare Act Regulations done according to the ILAR *Guide for Care and Use of Laboratory Animals*. The animal facility has Full-Accreditation with the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC-International).

Stent-graft placements will be done in adult farm swine. Smaller animals, such as Yucatan or Hanford minipigs, will not be used due to their slower weight gain (we are examining differences in weight gain so the farm swine with their rapid change in weight are expected to show a difference more readily than slower growing pigs), and also since they are smaller the arteries may be smaller and technical placement of the stent-graft may be more difficult.

Farm swine are an excellent model of obesity[27] and will gain about a pound a day when fed liberally. They are also large enough to be treated with the prosthesis, in contrast to smaller animal models. Pig mesenteric arterial anatomy is similar to humans and has been well-characterized angiographically and pathologically[13]. In the pig, a celiac, "cranial" mesenteric artery, and "caudal" mesenteric arise from the abdominal aorta, with the "cranial" mesenteric artery supplying most of the small intestine to the ascending colon[13].

Pigs will be observed for dietary intake for 3 days prior to the procedure by weighing all dispensed food and subtracting that not consumed, and pigs will also be weighed pre-procedure. On the day of the procedure, animals will receive a dose of 325 mg aspirin orally, and then anesthesia will be induced with Telazol (tiletamine hydrochloride 50 mg/mL, zolazepam hydrochloride 50 mg/mL) 6 mg/kg and Rompum (23 mg/mL, (xylazine hydrochloride) by intramuscular (IM) injection and sodium pentothal to effect (20mg/kg) intravenously (IV), and then maintained under isoflurane gas anesthesia. Preoperatively, the animals also will be given Atropine 0.05 mg/kg, and buprenorophine (0.01 mg/kg intramuscularly (IM)) for pain. They will be placed supine in a sterile operating room environment, and the skin disinfected first clipping the hair around the surgical area in both groin regions followed with alternating scrubs with providone-iodine scrub and alcohol, and then with povidone-iodine solution. Access to one or both femoral arteries will be performed by cut down after assurance of adequate anesthesia. Once dissection of the common femoral artery is done, animals will be randomized to one of two treatment groups. For the control group, this will be the extent of the sham procedure, and the incisions will be closed.

For animals randomized to receive the stent-graft and flow restriction, once the common femoral arterie(s) are dissected free, vessel loops will be placed proximally and distally. Puncture of the common femoral artery(ies) will be done using an 18 G or 19G hollow-core needle, and a guide wire placed under fluoroscopic guidance into the upper abdominal aorta. A vascular sheath will be placed and connected to a flush of half normal saline at an infusion rate of 15-30 milliliters/hour. A flush catheter will be placed through the sheath and a flush abdominal aortogram obtained to map out the blood supply to the intestine. Selective catheterization of the gastroduodenal artery and superior ("cranial") mesenteric artery will be done with a shaped catheter and arteriography done of those circulations.

For active treatment group animals, occlusion of the gastroduodenal artery will be done proximally with coils placed transcatheter. The endovascular prosthesis will be placed in the superior ("cranial") mesenteric artery and deployed. The endoprosthesis is designed to inflate like a dumbbell, narrow in the middle but wide at its ends. The approximate lumen diameter on deployment will be 2 mm in the middle and 6 or 7 at the ends.

The sequence of events that include placement of the stent-graft in the cranial mesenteric arteries is as follows:

1. Stent-graft deployed in cranial mesenteric artery in its most constricted configuration with a lumen of 1-2 mm, having a dumbbell shape when looked at in longitudinal section
2. Stent-graft dilated until resting systolic pressure gradient is reduced to approximately 10-20 mm Hg

3. Vasodilation performed with tolazoline 25 mg intra-arterial in the cranial mesenteric artery to record change in resting systolic pressure gradient (this may be important to correlate with outcomes such as weight loss or adverse events as it correlates to the post-prandial pressure gradient)
4. If at any time during or after the procedure the pressure gradient is too high at rest and/or symptoms are too severe with eating or severe at rest, it can be completely reversed easily by dilation with an angioplasty balloon

Pressure measurements will be done distal and proximal to the prosthesis before and after injection of 25 mg of the alpha blocker tolazoline into the SMA. The resting gradient should be used as the endpoint for expansion of the stent graft—once the gradient is reduced to borderline hemodynamic significance (10-20 mm Hg systolic), dilation will stop. Tolazoline is a vasodilator and will augment any pressure gradient, and the gradient post-tolazoline may correlate to effectiveness at inducing ischemia after meals. The stent-graft lumen diameter will then be increased using angioplasty balloons if needed so that there is no or minimal gradient at rest (less than 10-20 mm Hg systolic). Final pressure gradients at rest and after tolazoline will be recorded to help monitor results vis a vis complications or weight loss, and to guide subsequent procedures. Subsequently, wounds will be closed using absorbable sutures beneath the skin (2-0 through 4-0 Vicryl, Ethicon/Johnson&Johnson, Warren, NJ) and staples for the skin, and animals will then emerge from anesthesia.

The animals will be monitored for two hours post-op to monitor behavior and level of activity to make sure that the animals have completely recovered from anesthesia. They then will be evaluated q 12 hours and given analgesia, buprenorphine 0.01mg/kg IM for 24 hrs for pain. They will receive aspirin 325 mg orally each day for platelet inhibition, anticoagulation is not done in clinical practice for humans with stents grafts and won't be done.

Pigs will be handled according to the National Science Foundation's Guide for the Care and Use of Laboratory Animals. Pigs will be observed for signs noted in the 1992 report, "Recognition and Alleviation of Pain and Distress in Laboratory Animals", and these findings will be noted as adverse events and reported in the safety section of the manuscript describing the study's results. Species-specific signs of pain and distress in pigs include hiding, increased attempts to avoid handling, increased squealing when approached or held, increased vocalization, poor gait, separation from the group, and unwillingness to move. Anorexia, which can be a sign of pain or distress in pigs, will be of poor discriminatory value in this experiment because of the goal of reducing food intake. If signs are observed consistent with severe pain or distress, such as hiding or unwillingness to move, repeat angiography and pressure measurements will be done. If the pressure gradient has increased since the procedure was done, the stent-graft or artery may be dilated to reduce the gradient. If the artery is thrombosed, or if the revascularization attempt is unsuccessful and these signs of severe distress are not relieved within 24 hours, pigs will be euthanized and autopsy done to evaluate intestinal viability grossly.

The pigs will be closely monitored for 7 days for changes in activity, behavior, eating and watering habits. If the pig is found to not be eating or to be experiencing any discomfort, the veterinarian will be consulted and additional doses of buprenorphine may be administered at their discretion. Euthanasia will be performed in an instance were the animal is found to be in significant distress or discomfort, continuing decreased food/water intake, or exhibiting lethargy despite treatment at the discretion of the veterinarian in consultation with the investigators.

Thereafter, the animals will be checked daily for any changes in activity, behavior, eating habits, urine or feces output. If any change is noted, appropriate evaluation will be done to determine if the animal is experiencing any pain or if there is an infection present (infection will be evaluated by visual examination of surgical sites for abnormal changes as well as temperature evaluation). They will be

monitored for dietary caloric intake for 3 day periods at one week and one month post-procedure. Weighers will be trained on the laboratory standard method of weighing, including weighing on a consistent time of day, and will be blinded to the treatment group. After 60 days, pigs will be weighed and sacrificed. Gross inspection of the bowel and mesenteric artery endoprosthesis done for descriptive purposes, including the presence of bowel ischemia, stricture, infarction, intraarterial thrombus or intimal hyperplasia.

D.3 Sample Size Estimate

Sample size was estimated based on the anticipated difference between groups at 60 days (t-test). It is anticipated that the use of repeated measures ANOVA at analysis will be more sensitive and so the calculated sample size represents a conservative estimate of that required. The following assumptions are made:

- The mean weight for the population of pigs at baseline is 160 lbs
- After one month of ad lib feeding, the control group mean weight is estimated conservatively at 170 lbs
- After one month of ad lib feeding, the treatment group mean weight will be 150 lbs
- The group standard deviation is 12 lbs
- The effect size, or standardized difference, ={(170-150)/12}=1.67

H_o: $\mu_{SH} = \mu_{ST}$
H_a: $\mu_{SH} \neq \mu_{ST}$

Where μ_{ST} is the primary endpoint estimate for the reducing stent-graft group and μ_{SH} is the primary endpoint estimate for the sham group at 60 days. The null hypothesis is that the sham group and stent group mean weight will not differ significantly at 60 days. The alternative hypothesis is that there will be a statistically significant difference in the mean weight of the stent group compared with the sham group at 60 days. Rejection of the null hypothesis will signify that the weight change between the two groups is significantly different. **Given the above, with an α of .05 and power of 90%, a sample size of 18 (9 per group) evaluable subjects is needed (EaST 2000 software, Cytel Corporation, Cambridge, MA).** We have inflated the sample size by two (10%) to account for study subject drop out such as for example due to technical failure of stent-graft implantation procedure and complications of either treatment, or drop out due to other unanticipated causes.

D.4 Statistical Analysis:

Data will be collected in laboratory notebooks and entered into a computer database (Access 2000, Microsoft, Redmond, WA) designed for this project. Data will be analyzed using StatView v.5.0.1 statistical software (SAS Institute, Cary, NC).

Primary endpoint:

Change in weight will be compared between treatment groups using repeated measures ANOVA with Group as a fixed effect.

Secondary endpoints:

1. Estimate of dietary caloric intake—Pigs will be fed *ad lib*, and excess amounts of feed will be left in the pen with each pig. Caloric intake will be calculated by measuring standard feed prior to filling the feed dispensing bin, and then at the end of a three day period measuring how much is left in the bin and in the pen, and therefore how much was consumed. Caloric equivalents will be calculated according to the feed manufacturer's information. The change in average caloric intake over the 3

day period pre-intervention compared with one week and one month later will be compared using a t-test.

2. Adverse events—Adverse events will be categorized as serious (death, bowel infarction, infection, hemorrhage) or nonserious (diarrhea, aversion to food, reduced activity), and will be monitored in the post-operative period as well as throughout the survival period. Species-specific signs of pain and distress in pigs include hiding, increased attempts to avoid handling, increased squealing when approached or held, increased vocalization, poor gait, separation from the group, and unwillingness to move will also be monitored as study endpoints as well as to help ensure humane treatment of the animals. These adverse events will be recorded so that risks of the proposed treatment can be understood, and any benefits in terms of weight loss be understood in the context of the risk of the treatment.

The quantitative milestones for this Technology Development Plan are as follows:

1. Laser cutting and ablation waste removal of the first prototype (first generation)
2. Bench tests of the first prototype(s) demonstrating successful controlled variable diameter stent inflation without stent asymmetry and easy balloon removal from the stent
3. Successful bonding of PTFE "skin" to prototype stent(s)
4. Bench tests of stent-graft (stent and bonded "skin") showing successful controlled variable diameter stent inflation without stent asymmetry and easy balloon removal from the stent
5. Re-design if necessary of stent-graft
6. Repeat bench tests
7. Successfully deploy second generation stent-graft(s) in pig mesenteric arteries
8. Modifications of system in response to first animal use
9. Deploy system/perform procedure in 10 pigs' mesenteric arteries and complete sham procedure in 10 pigs
10. Complete 60 day follow up of all pigs

The General Research Plan for Phase II is:

Depending on the success of Phase I, Phase II could consist of improving stent-graft design and more preliminary investigation in animals, or could be safety studies in human subjects. Once the results of Phase I are in, if the technology development went smoothly with compelling preliminary results (significant difference in weight loss between the treatment groups with few adverse events) we can request an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) to proceed to human subjects. This would most likely take the form of safety studies in a limited number of individuals. The design of such a study, data collected, and endpoints would largely be dictated by the FDA. Subsequent "Phase II" would then include clinical trials of first safety, then efficacy, and probably two clinical trials would be required for FDA approval to market the device.

Software Sharing Plan

We anticipate no software development as part of this project.

IGI Systems/Nonproprietary Interface

The imaging-guided intervention proposed in this study can be done using any fluoroscopic imaging equipment and does not require proprietary equipment or software to perform.

D.5 Key Personnel

Dr. Timothy Murphy is the Director of Quequechan Engineering, Inc., and an interventional radiologists practicing in Providence, Rhode Island. He is the Director of the Vascular Disease Research Center at Rhode Island Hospital, and a Professor, Research Track, of Diagnostic Imaging at Brown Medical School. He has over 13 years of experience as an interventional radiologist and performs procedures similar to those proposed as part of this experiment on a regular basis. He is a fellow of the Society of

Interventional Radiology, the American Heart Association, the Society of Vascular Medicine and Biology, and the American College of Radiology. He is the principal investigator of the CLEVER multicenter randomized clinical trial (Claudication: Exercise Vs. Endoluminal Revascularization, NHLBI R01 HL077221), and co-principal investigator of the CORAL Study (Cardiovascular Outcomes with Renal Atherosclerotic Lesions, NHLBI R01 HL071556-01). In addition to participating in prototype design and development, Dr. Murphy will perform the animal experiment as principal investigator, will collect and analyze data, and report study results.

Dr. Lamar Bullock received a Ph.D. in physics from Michigan State University and is an Adjunct Professor of Physics at University of Massachusetts-Dartmouth, and is the director of the photonics laboratory that includes the IX-300 Micro-Machining Laser. Dr. Bullock was formerly president of Boston Laser Technology, where he developed a unique excimer laser-based manufacturing process. He also designed and built laser imaging equipment to apply this process to volume manufacturing of a coronary stent for a company, Buckbee-Mears (St. Paul, MN), that was developing stents for Cordis/Johnson&Johnson (Warren, NJ), one of the largest manufacturers of vascular stents in the world. This project required close coordination with the stent designers to make optimal use of a new laser-based manufacturing process.

SUMMARY STATEMENT

Christine Densmore
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(Privileged Communication)

Release Date: 03/23/2006

Application Number: 1 R41 DK076502-01

MURPHY, TIMOTHY P MD
RHODE ISLAND HOSPITAL
DEPT OF DIAGNOSTIC IMAGING
593 EDDY STREET
PROVIDENCE, RI 02903

Review Group: ZRG1 DIG-A (10)

Meeting Date: 03/10/2006
Council: MAY 2006
Requested Start: 07/01/2006

RFA/PA: PA06-007
PCC: NCD DDSB
Dual PCC: HHVOVN
Dual IC(s): HL

Project Title: Percutaneous mesenteric arterial flow modulation as treatment for morbid obesity

SRG Action: **
Human Subjects: 10-No human subjects involved
Animal Subjects: 44-Vertebrate animals involved - SRG concerns

Project Year	Direct Costs Requested
1	220,360
TOTAL	220,360

**NOTE TO APPLICANT: As part of the initial scientific merit review process, reviewers were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. At the study section meeting, those applications were discussed and assigned a priority score. All other applications, including this application, did not receive a score. Provided is a compilation of reviewers' comments prepared prior to the meeting, without significant modification or editing by NIH staff.

BUDGET MODIFICATIONS

1R41DK076502-01 MURPHY, TIMOTHY

CRITIQUE 1:

SIGNIFICANCE: The authors have identified morbid obesity as a clinically important problem for which optimal treatment has not yet been identified. As such, novel treatment methods are needed. The significance of the current proposal is the novel idea which the authors intend to study as a new and different approach to treatment of morbid obesity, that of the induction of visceral ischemia.

APPROACH: Chronic visceral ischemia is a serious condition in which blood flow to the small and large intestine is impaired; usually from atherosclerotic narrowing. Significant occlusion of two of the three visceral arteries (celiac, superior mesenteric, inferior mesenteric) is needed to induce chronic visceral ischemia. Although usually painful stimuli, such as cutting with a knife, or stabbing with a needle do not induce pain in the intestines, the two most powerful inducers of pain are distention and ischemia. In patients with chronic visceral arterial occlusion, blood flow to the intestines can't increase in response to a meal. Mucosal flow comprises 50% of flow to the intestines in the fasting state, and this increases to 75% after a meal. The progression from minor symptoms to transmural infarction is unpredictable and mortality of transmural infarction is 80%.

The inability to increase visceral blood flow and the resultant ischemia in response to a meal creates pain, which in turn causes affected individuals to avoid food, or eat only small amounts – "food fear". Consequently, affected individuals lose weight. It is this aspect that the authors intend to exploit in their admittedly novel approach to the treatment of morbid obesity. Turning conventional therapy on its head, instead of using stents to open narrowed vessels, this proposal seeks to place stents to decrease visceral blood flow, inducing "food fear". The concept of establishing a negative stimulus-response in the morbidly obese is not new, as the pouch restriction and distention in response to overfeeding, or the gas bloat and diarrhea seen after eating too many sweets associated with gastric bypass are similar examples.

There are four aims. The first proposes to create balloon-expandable stents for purposes of this proposal. There is no discussion of why currently existing stents might not work, at least for proof of principle. The authors present *in situ* data for a 30 kg swine that gives the size of the cranial mesenteric artery (analogous to human superior mesenteric artery) as 6 mm outer diameter. It is probably important to know whether in the fed state the proximal artery dilates as well as the downstream vascular bed. Most atherosclerotic lesions are fixed, unlike normal arteries. This could be evaluated *in vivo* with duplex ultrasonography.

Aim 2 is to study mesenteric arterial flow in the swine visceral circulation to understand collateral pathways of importance and devise ways to occlude these pathways. I note that the authors appear to believe that the 6 mm artery in the 30 kg swine is somewhat at the limits of their catheterization abilities, so how small collaterals are likely to be embolized is not clear. There is no plan for obtaining flow data that might suggest how much limitation is necessary to effect the desired weight loss. There are no specific experiments presented to show exactly how the authors intend to satisfy Aim 2.

Aim 3 is to use data supplied from the first two aims to perform a study in which adult swine are randomized to reducing stent or sham catheterization. The randomization is said to be after arteriography, the rationale for which is unclear. They will then observe the animals to see if one group gains more weight. There appear to be 5 swine in each group, however there is no discussion of how these sample sizes were generated. Although maintenance of swine for such a study is resource intensive, a biostatistician should help decide how many should be treated in each group for differences in weight loss. The authors are predicting a 20 pound difference in weight, but there is no rationale for this choice. The 20 pound difference is a delta of one pound per three days. There is no discussion of what signs they will be observing to determine if the swine are in distress (e.g. manifest food fear).

Aim 4 will use tolazoline, an alpha adrenergic blocker, to mimic increased flow associated with a meal. The plan is to first place the stent, then dilate the luminal diameter so the resting pressure across the stent is nil. Then, tolazoline, 25 mg, will be used to see if a pressure gradient can be detected. The authors do not discuss what they intend to do if no gradient can be seen after infusion of the tolazoline.

INNOVATION: This is an innovative idea, and looks at the treatment of morbid obesity in an entirely novel way.

INVESTIGATORS: Appear to have the expertise to carry out the required studies.

ENVIRONMENT: Adequate.

VERTEBRATE ANIMALS: Appears appropriate. As a part of the scientific design, however, more detail on exactly how the investigators will score pain and food aversion must be addressed.

OVERALL EVALUATION: The strength of this application is the novelty of the approach and the stent fabrication expertise of the investigators. Weaknesses include a basic conceptual issue about whether it is ethical to induce pain as an approach to trying to get patients to lose weight. Further, given the significant degree to which arterial occlusion is necessary in humans to get chronic visceral ischemia, it is unclear whether adequate occlusive stenting can be done safely. All issues of translation into the clinical setting aside, for the reasons mentioned above, it is unclear that the swine studies proposed will answer the question of whether or not this is a viable approach.

BUDGET: I question the charge of administrative (secretary/clerical). Otherwise the budget appears adequate.

CRITIQUE 2:

SIGNIFICANCE: Obesity is a significant health problem in the US and worldwide. Therefore, developing new therapeutic modalities for inducing weight loss is a very relevant area of investigation. However, in this application the PI is proposing to introduce a stent into the arterial blood vessels of the small intestine to induce a serious condition resembling chronic intestinal ischemia. This approach is likely unfeasible and unethical.

APPROACH: This is the first submission of an R41 STIR application to develop a new treatment modality for obesity based upon reducing blood flow to the small intestine. The approach this investigator is taking to address this important issue is seriously flawed since the PI is effectively suggesting the induction of a serious disease state, i.e., chronic abdominal angina and mesenteric ischemia to induce weight loss. Thus, the weight loss will derive from the pathological condition associated with severe symptoms in many cases, including diarrhea, malabsorption and significant abdominal pain. How would one control for the amount of ischemia generated in the small intestine to avoid, for example, intestinal infarction? Unfortunately the PI has not discussed any of these important issues related to the applicability of this methodology to the human condition within the experimental design of this application.

INNOVATION: This proposal is certainly innovative; however, it is unlikely to be applicable to obese patients without serious complications.

INVESTIGATORS: Dr. Murphy is a professor of research at Brown Medical School. He is an established investigator in the field of vascular biology, with expertise in vascular stenting. He is collaborating with Quechan Engineering, Inc. It is unclear from the proposal who in this company is collaborating in these studies. Dr. Murphy is certainly qualified to perform these studies.

ENVIRONMENT: Appropriate as described.

VERTEBRATE ANIMALS: The five points that are required for vertebrate animals are not appropriately described.

OVERALL EVALUATION: This is a new R41 STIR application to develop a novel therapeutic modality to treat obesity. The main problem with this grant proposal is that the PI is proposing to induce a serious disease state in obese patients to cause them to fear food, experience serious symptoms of intestinal ischemia and then lose weight. This proposal raises significant ethical concerns and there is highly unfeasible. Therefore, the proposal is not recommended for further consideration.

BUDGET: Appropriate as described.

CRITIQUE 3:

SIGNIFICANCE: Morbid obesity is a significant public health problem and is responsible for placing an enormous financial burden on our society. It is also a major risk factor for cardiovascular diseases and diabetes. The main therapy against obesity consists of various weight-loss programs based on stimulating exercise and restricting dietary intake. Other more radical treatments are surgically based and include gastric bypass. Such treatments are not free of complications (1-2 % mortality) and are generally reserved for the most severely obese patients. The investigators propose a radically new method based on well-known endovascular techniques used commonly to treat patients with vascular diseases. This approach, placing a stent-graft in the superior mesenteric artery to reduce blood flow and thus create a controlled form of mesenteric ischemia, is somewhat innovative and if successful could prove quite significant despite a number of major problems and ethical consideration.

APPROACH: The goal of the proposal is to induce a "controlled" form of mesenteric ischemia by placing a stent-graft in the superior mesenteric artery in order to limit food intake. The resultant "food fear" would force obese patients to eat small meals to avoid causing excruciating abdominal pain due to the newly created mesenteric ischemia. There are a number of major problems with this proposal:

Stent graft design: There are a number of commercially available stents and stent grafts, yet the investigators do not provide any explanation as to why they need to design a new type of stent, especially in view of the fact that such stent grafts have been used for the same purpose (i.e. reducing blood flow) in the case of Transjugular Portosystemic Shunts (TIPS) for patients with portal hypertension. The same dumbbell shape that the investigators want to test to induce mesenteric ischemia has already been used successfully with commercially available stent grafts to reduce porto-systemic venous flow. The rationale for a new stent design must be provided.

Experimental protocol: The need for randomization after the diagnostic angiogram is not explained and does not appear justified unless it is done to control for the effects of the surgery.

Unexplained potential problems: No remedy to potential problems encountered during the conduct of the proposed experiments is given. For example, what if the stent graft does not reduce blood flow enough? Or if on the contrary, the stent graft is too occlusive, which can happen in vessels of that size (6 mm)? The problem of distal flow is not addressed at all. Not only does it have practical implications from the standpoint of successfully completing the experiments, but it does also have major ethical considerations if the degree of flow reduction can not be totally controlled. It could lead to irreversible ischemia requiring some form of surgical intervention if at all.

Ethics: There should be serious reservations about conducting the proposed experiments in pigs given the fact that evaluating and quantifying the degree of mesenteric ischemia-related pain and "food fear" is not addressed at all by the investigators. It might not be feasible to do so, but at the very least the investigators should have studied that problem in detail. Translating this method to humans is even more problematic from the ethical standpoint. How can we justify inducing severe abdominal pain every

time someone eats? Furthermore, the problem of irreversibility i.e. in case the pain is intolerable for the patient, is not addressed at all.

INNOVATION: The concept of treating morbid obesity via endovascular means is highly innovative, although it is extremely controversial ethically. However, the use of stents or stent-grafts as in this case to limit flow in a vascular structure is not new as it has been used not uncommonly for patients suffering from portal hypertension treated with Transjugular Portosystemic Shunts (TIPS). Some of these patients can experience a high degree of encephalopathy as a result of increased flow from the portal vein to the hepatic veins. In such instances (published reports by Haskal), a stent-graft can be shaped as described in the current protocol in order to reduce blood flow without causing complete occlusion.

INVESTIGATORS: The PI is a well respected interventional radiologist with a vast experience in the field of peripheral vascular interventions. His team should be able to accomplish some of their goals, especially the creation of a stent graft, but it is not sure whether the remaining goals will be achieved.

ENVIRONMENT: Appropriate for the scope of the studies described in the proposal.

VERTEBRATE ANIMALS: Serious reservations about the experimental design of the study involving the animals, specifically Aims 2-4. No explanation is provided to justify the number of animals in terms of reaching statistical significance. The investigators did not address how they will evaluate mesenteric ischemic pain or quantify food fear in the pigs. Measuring weight loss is perhaps scientifically relevant but certainly not ethically correct. This must be dealt with in some fashion. The proposal has not yet been submitted to ACUC.

BIOHAZARDS: No issue.

OVERALL EVALUATION: Although this proposal deals with a critically important issue plaguing our health care system, namely obesity and more specifically morbid obesity, it is far from convincing from the scientific standpoint. The notion of using endovascular minimally invasive techniques to create a "controlled" form of mesenteric ischemia to reduce food intake through induction of food fear may be innovative but it is largely untested and the proposal is filled with unanswered questions that may prove to be insurmountable. The experimental design is also generally weak and potential problems are not dealt with appropriately.

BUDGET: Appropriate except the 50% salary support for an administrative secretary, as it does not appear clear at all what the need for this person will be throughout the work proposed in this application.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
ZRG1 DIG-A (10) B
March 10, 2006

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BETHESDA, MD 20892

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

NOTIFICATION OF SCIENTIFIC REVIEW ACTION

Release Date: 03/23/2006

MURPHY, TIMOTHY P MD
RHODE ISLAND HOSPITAL
DEPT OF DIAGNOSTIC IMAGING
593 EDDY STREET
PROVIDENCE, RI 02903

Our Reference: 1 R41 DK076502-01 ZRG1 DIG-A (10)

The scientific merit review of your application, referenced above, is complete. As part of this initial review, reviewers were asked to provide written evaluations of each application and to identify those with the highest scientific merit, generally the top half of applications they customarily review, for discussion at the meeting and assignment of a priority score. Your application did not receive a score. Unscored applications are neither routinely reviewed at a second level by a national advisory council or board nor considered for funding.

Enclosed is your summary statement containing the reviewers' comments. You should call the program official listed below to discuss your options and obtain advice.

Christine Densmore
(301) 402-8714
densmorec@extra.niddk.nih.gov

If you choose to resubmit, it is important to respond specifically to comments in the summary statement, as outlined in the instructions in the PHS 398 application kit (http://grants1.nih.gov/grants/funding/phs398/phs398.html).

Enclosure

cc: Business or institutional official of applicant organization

Director
151 Martine Street
Suite 121
Fall River, MA 02723-1514

SUMMARY STATEMENT

(Privileged Communication)

Release Date: 04/16/2007

PROGRAM CONTACT:
John Haller
301-451-4780
hallerj@mail.nih.gov

Application Number: 1 R21 EB007566-01

Principal Investigator

MURPHY, TIMOTHY P MD

Applicant Organization: QUEQUECHAN ENGINEERING, INC.

Review Group: ZEB1 OSR-B (M1)
National Institute of Biomedical Imaging and Bioengineering Special Emphasis Panel

Meeting Date: 03/14/2007
Council: MAY 2007
Requested Start: 07/15/2007

RFA/PA: EB06-003
PCC: AITD

Project Title: Percutaneous mesenteric arterial flow modulation as treatment for morbid obesity

SRG Action: **
Human Subjects: 10-No human subjects involved
Animal Subjects: 30-Vertebrate animals involved - no SRG concerns noted

Project Year	Direct Costs Requested
1	223,060
TOTAL	223,060

**NOTE TO APPLICANT: As part of the initial scientific merit review process, reviewers were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. At the study section meeting, those applications were discussed and assigned a priority score. All other applications, including this application, did not receive a score. Provided is a compilation of reviewers' comments prepared prior to the meeting, without significant modification or editing by NIH staff.

1R21EB007566-01 MURPHY, TIMOTHY

SCIENTIFIC REVIEW ADMINISTRATOR'S NOTE

DESCRIPTION (provided by applicant): Obesity is an epidemic in the U.S. More than half of the U.S. population is overweight, one-third are obese, and more than 5 million adults in the U.S. are categorized as morbidly obese (body mass index >40). Obesity is associated with increased cardiovascular disease risk and mortality. The BROAD, LONG-TERM OBJECTIVES of this project are to improve health in individuals with morbid obesity. The SPECIFIC AIMS are to test a novel approach at inducing weight loss in an animal model by reducing blood mesenteric arterial blood flow thereby not allowing increases in mesenteric blood flow required for digestion after a large meal, the purpose of which is to result in a behavioral change to avoid over-eating. The RATIONALE is that because blood flow in the mesenteric circulation normally increases 3-fold in diastole (the dominant part of the cardiac cycle) after meals, it should be possible to induce a state where blood flow is adequate to maintain bowel viability without symptoms at rest, but not sufficient to accommodate the large increase in flow that is necessary after meals, resulting in abdominal pain and/or diarrhea after large meals. This will result in behavior changes such as avoidance of eating large amounts, thereby producing weight loss. Mesenteric blood flow modulation will be done by a combination of vascular occlusion of the gastroduodenal artery (GDA) and variable flow reduction of the superior (cranial) mesenteric artery (SMA) in pigs using a proprietary stent-graft designed for this purpose, to be placed using percutaneous interventional techniques. The HEALTH-RELATEDNESS is that weight loss lowers the risk of cardiovascular and other health adverse events, and improves quality of life. If effective, the proposed treatment would be appealing for those who are not candidates for invasive gastric bypass surgery, and may prove to be a lower risk alternative to gastric bypass surgery. The RESEARCH DESIGN AND METHODS would be to develop a fabric-covered vascular stent-graft for percutaneous, fluoroscopically-guided placement into the superior (cranial) mesenteric artery of pigs, and occlusion of the GDA with coils. After the prototype is developed and bench-tested, it will be introduced into 10 adult swine, with 10 also undergoing a sham procedure. Post-procedure course will be monitored including dietary intake and weight up to 2 months. We will look for a statistically significant difference in weight change score as a continuous variable as the primary endpoint, and will also examine adverse events, and daily dietary caloric intake pre- and post-procedure. Principal Investigator: Murphy, Timothy, Patrick More than 5 million adults in the U.S., 5% of the adult population, meet the definition of morbid obesity. There may be as many as 2 million people in the U.S. who would be candidates for the proposed treatment, which may be possible with lower cost and substantially lower morbidity and mortality than gastric bypass surgery.

CRITIQUE 1:

Description: The authors propose to build and investigate a new covered stent with constricted central diameter so as to impose gastric ischemia as a means to treat morbid obesity.

SIGNIFICANCE:
Although obesity is an extremely important national problem, it has primarily behavioral and cultural causes. Nevertheless, the use of a more convenient, cheaper, less invasive procedure such as the authors propose has the potential to replace existing invasive surgical procedures and to enable a larger number of people to be treated with a physical intervention for something that is essentially behavioral in nature. Also as the authors admit there are questions of ethics, purposeful induction of pain, and risks of infarction that arise and they argue that the benefit is worth the risk. There is a question as to how many patients would submit to a procedure to induce ischemia where, as the authors state, "the symptoms of this disease include weight loss, malabsorption, anorexia, food fear, and diarrhea." These somewhat contradictory justifications for the project tend to detract from one's enthusiasm for it in terms of its significance.

APPROACH:
The authors approach is to design, manufacture, and test a PTFE-covered, balloon-expandable stent that upon deployment can have a longitudinally-central diameter restriction to reduce blood flow to the superior mesenteric artery (SMA) and simultaneously to use coils to embolize the gastroduodenal artery (GDA). While the authors should be able to achieve their technical goals of creating such a stent and deploying it in a number of test animals, the design procedure appears to be somewhat of a trial-and-error approach. For a new stent of this kind it would seem that to have any justification for long term efficacy and safety one would have to demonstrate through computer simulations using finite element analysis (FEA) that a particular design could achieve its physical goals. Most covered stents and stents in general are placed in abnormal or diseased vessels so one would be concerned about matching the compliance and other mechanical properties of such a new stent with the normal vessel that it is intended to be deployed in. One is also unconvinced that the procedure as the authors claim is totally reversible by simply balloon expanding the new stent so as to enlarge the central diameter. What started out as a normal healthy vessel will never be as such again and one is uncertain as how such a vessel might react years later if it were desired to undo the treatment because the patient might have matured or may no longer have the behavioral problems that originally caused the obesity. Details of the use of the coils to occlude the GDA were also lacking as well as possible long term results from this apparently irreversible procedure.

It is not even certain that the procedure would necessarily have the desired effects in the intermediate term. If there were collateral blood flow then less ischemia would be induced and there might be minimal effect. If there were minimal collateral flow then the risk of infarction would seem to be greater.

There is also a question as to the experience, expertise, and capability of laser cutting the stents in-house since this usually requires great accuracy and dedicated equipment and personnel. It might be less expensive and more advantageous to contract out the laser cutting to facilities that do only such work and who would return electro-polished sample quantities without the learning curve that the in-house facility would appear to have to go through. Additionally, there is no detailed discussion of a possible special balloon that might be needed to expand this new stent so that the diameters are not uniform. Most existing balloon-expandable stents use a non-compliant balloon to expand stents to a somewhat uniform diameter perhaps with a bit of dog-boning; however, for the stent with constriction in middle as proposed by the authors, either a compliant balloon with difficult to predict final expanded diameter, or a non-compliant specially designed balloon to fit the desired final shape would have be used. In either case there are technical problems that the authors do not seem to have considered in detail.

INNOVATION:
The design of the new stent is somewhat innovative; however, much of the technology they propose for the stent presently exists. The application to purposely create blood flow constriction in a normal vessel appears original.

INVESTIGATORS:
Dr. Timothy Murphy is a prominent vascular interventional radiologist who is a principal in the small company Quequechan and he is the director of Vascular Disease Research at Rhode Island Hospital and on the faculty of Brown University. His commitment is 10%. His experience and credentials would appear to be quite appropriate for the clinical and leadership role he plays in the project. L. Bullock, PhD of U. Mass-Dartmouth is a physicist and manager of the Photonics Lab; however, he has no research publications listed since 1973 in his very brief biosketch. It is stated in the proposal that he had some experience in laser cutting stents at one time but the extent of his capability in FEA and leading the design and manufacture of the stents is hard to evaluate from what is stated in the proposal. Other work is to be done by graduate students, laboratory personnel at Rhode Island Hospital animal facilities, and an administrative assistant to Dr. Murphy.

ENVIRONMENT:

Environment appears adequate to the tasks proposed although there is some question regarding the approach, experience, and perhaps the resources needed to adequately laser cut the stents.

OVERALL EVALUATION:
It would seem that even if the proposed stent were able to be satisfactorily made and deployed, the simple animal experiments envisioned to see if a population of 10 farm pigs can be induced to eat less would be hardly conclusive regarding long term efficacy and safety in humans. There are also some questions regarding the techniques proposed for designing and deploying the new stents with the correctly designed balloons as well as some question about the use of in-house facilities for laser cutting the stents. Basically, the authors propose to induce gastric ischemia by constricting healthy vessels with a permanently deployed stent and with embolic coils. It is difficult to be enthusiastic about a proposal to make more accessible a potentially risky alternate physical treatment for what is essentially the behaviorally-caused condition of obesity.

CRITIQUE 2:

SIGNIFICANCE:
The PI proposes to develop a stent graft that can be placed in the superior mesenteric artery endovascularly under image guidance. The stent graft will be balloon inflatable and when inflated will take on a "dog bone" shape with a stenosis in the center such as to restrict blood to the smaller arteries supplying the bowel. The premise is that by constricting the flow through the superior mesenteric it will create a condition similar to the clinical condition of chronic mesenteric ischemia. Patients with that condition have to adapt their eating habits to the condition by eating small amounts of food frequently and therefore lose weight. Obesity in the US has reached epidemic proportion and approximately $100 billion is spent annually for the treatment of obesity related diseases. Combating obesity is significant.

APPROACH:
The PI proposes two specific aims. In the first aim they will develop a variable diameter stent-graft for introduction in the pig superior mesenteric artery in conjunction with selective embolization of collateral arteries to reduce mesenteric flow. In the second specific aim the device will be placed in a cohort of barnyard swine to compare their weight and caloric intake to a cohort of controls.

The application is essentially proposing to develop a device for a non established animal model and then see if an animal model can be established. What should be done first before embarking on the road of device development is to demonstrate that an animal model exists by using simple coarctations around the mesenteric artery. Also, in the methods section the application does not talk about embolization of collaterals despite the fact that it appears in the first specific aim.

INNOVATION:
BioMEMS Highly innovative application

INVESTIGATORS:
The PI is experienced in endovascular procedures and implantation of stents. The faculty is experiences in the design and fabrication of stents and stent-grafts.

ENVIRONMENT:
The available facilities of the proposing organization and partner are sufficient to execute the proposed project.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISKS:
N/A

GENDER, MINORITY AND CHILDREN SUBJECTS:
N/A

VERTEBRATE ANIMALS:
No concerns, IACUC approval pending.

BIOHAZARDS:
No concerns

OVERALL EVALUATION:
Strengths: Very innovative proposal, attacking obesity from an unorthodox direction.

Weaknesses: The percent stenosis required for significant flow restriction through the mesentery artery is very high and it is not clear that it can be achieved by varying the stent strut properties alone. There is no established animal model for weight modulation using mesenteric ischemia. The technical challenges in the fabrication of a device that will dialate less than 50% in the center compare to the ends are not laid out and while it is noted that design modifications will be required, solutions are not proposed.

BUDGET:
Reasonable for the amount of work proposed.

CRITIQUE 3:

The stated long-term objective of this application is to improve health in individuals with morbid obesity (Body mass index >40). The specific aims are to test a novel approach at inducing weight loss in pigs by diminishing mesenteric blood flow and inducing an iatrogenic state of mesenteric insufficiency. This is accomplished by percutaneous stent placement into the Superior Mesenteric Artery (SMA) and occluding other arteries selectively by embolization.

Study animals will be compared to animals treated by sham procedure by monitoring dietary intake and weight over two months. Obesity and related medical illness is on the increase in N. America. Bariatric surgery (Gastric Bypass) is an accepted corrective measure in patients who fail tradition weight loss plans and have weight-related co-morbid illness. Minimally invasive alternatives, like the "Lap Band" are also available. Chronic mesenteric ischemia often results in post-prandial discomfort, sidophobia, and weight loss. However, injury or occlusion of the SMA and other mesenteric vessels can result in significant morbidity and mortality. This proposal is IACUC approved. Human subjects approval would require strong pilot data suggesting safety and efficacy.

SCIENTIFIC REVIEW ADMINISTRATOR'S NOTE:

VERTEBRATE ANIMALS (Resume): ACCEPTABLE

NIH announced implementation of Modular Research Grants in the December 18, 1998 issue of the NIH Guide to Grants and Contracts. The main feature of this concept is that grant applications (R01, R03, R21, R15) will request direct costs in $25,000 modules, without budget detail for individual categories. Further information can be obtained from the Modular Grants Web site at http://grants.nih.gov/grants/funding/modular/modular.htm

MEETING ROSTER

National Institute of Biomedical Imaging and Bioengineering Special Emphasis Panel
NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING
ZEB1 OSR-B (M1) R
March 14, 2007 - March 15, 2007

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

NOTIFICATION OF SCIENTIFIC REVIEW ACTION

Release Date: 04/16/2007

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Our Reference: 1 R21 EB007566-01 ZEB1 OSR-B (M1)

The scientific merit review of your application, referenced above, is complete. As part of this initial review, reviewers were asked to provide written evaluations of each application and to identify those with the highest scientific merit, generally the top half of applications they customarily review, for discussion at the meeting and assignment of a priority score. Your application did not receive a score. Unscored applications are neither routinely reviewed at a second level by a national advisory council or board nor considered for funding.

Enclosed is your summary statement containing the reviewers' comments. You should call the program official listed below to discuss your options and obtain advice.

PROGRAM CONTACT:
John Haller
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If you choose to resubmit, it is important to respond specifically to comments in the summary statement, as outlined in the instructions in the PHS 398 application kit (http://grants1.nih.gov/grants/funding/phs398/phs398.html).

Enclosure

cc: Business or institutional official of applicant organization

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Dr. Bonnie Burgess-Beusse is a Scientific Review Administrator in the Digestive Sciences Integrated Review Group. Dr. Burgess-Beusse received her Ph.D. in molecular and human genetics from Baylor College of Medicine in Houston. Her research there focused on transcriptional regulation of the acute phase response to inflammation. Subsequently, she was a postdoctoral research fellow at the National Institute of Diabetes and Digestive and Kidney Diseases, where she worked in the Laboratory of Molecular Biology studying vertebrate chromatin insulator elements, DNA sequences that recruit proteins to set up boundaries that separate independently regulated chromatin domains. She is currently helping to coordinate the review of the Digestive and Respiratory Sciences Small Business grants.

Last Update 3/31/2008

[Organizational Chart]

Any content changes, comments or suggestions should be provided to the CSR IT Directory@mail.nih.gov

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Related Articles, Links
Pollack MJ, Chak A.

Quality in endoscopy: it starts during fellowship.
Gastrointest Endosc. 2008 Jan;67(1):120-2. No abstract available.
PMID: 18155433 [PubMed - in process]

2:

Related Articles, Links
Rollins AM, Ung-Arunyawee R, Chak A, Wong RC, Kobayashi K, Sivak MV Jr, Izatt JA.

Real-time in vivo imaging of human gastrointestinal ultrastructure by use of endoscopic optical coherence tomography with a novel efficient interferometer design.
Opt Lett. 1999 Oct 1;24(19):1358-60.
PMID: 18079803 [PubMed - in process]

3:

Related Articles, Links
Das A, Ben-Menachem T, Farooq FT, Cooper GS, Chak A, Sivak MV Jr, Wong RC.

Artificial neural network as a predictive instrument in patients with acute nonvariceal upper gastrointestinal hemorrhage.
Gastroenterology. 2008 Jan;134(1):65-74. Epub 2007 Oct 25.
PMID: 18061180 [PubMed - indexed for MEDLINE]

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Related Articles, Links
Kumon RE, Olowe K, Faulx AL, Farooq FT, Chen VK, Zhou Y, Wong RC, Isenberg GA, Sivak MV, Chak A, Deng CX.

EUS spectrum analysis for in vivo characterization of pancreatic and lymph node tissue: a pilot study.
Gastrointest Endosc. 2007 Dec;66(6):1096-106. Epub 2007 Oct 29.
PMID: 18028925 [PubMed - in process]

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Thompson CL, Khiani V, Chak A, Berger NA, Li L.

Carbohydrate Consumption and Esophageal Cancer:An Ecological Assessment.
Am J Gastroenterol. 2007 Nov 6; [Epub ahead of print]
PMID: 17986316 [PubMed - as supplied by publisher]

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Related Articles, Links
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Complete endoscopic closure of gastric defects using a full-thickness tissue plicating device.
J Gastrointest Surg. 2008 Jan;12(1):38-45. Epub 2007 Oct 24.
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Related Articles, Links
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Complete endoscopic closure of gastrotomy after natural orifice translumenal endoscopic surgery using the NDO Plicator.
Surg Endosc. 2008 Jan;22(1):214-20. Epub 2007 Sep 3.
PMID: 17786515 [PubMed - indexed for MEDLINE]

8:

Related Articles, Links
Atkinson M, Das A, Faulx A, Kinnard M, Falck-Ytter Y, Chak A.

Ultrathin Esophagoscopy in Screening for Barrett's Esophagus at a Veterans Administration Hospital: Easy Access Does Not Lead to Referrals.
Am J Gastroenterol. 2008 Jan;103(1):92-7.
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Related Articles, Links
Atkinson M, Chak A.

Unsedated small-caliber endoscopy--a new screening and surveillance tool for Barrett's esophagus?
Nat Clin Pract Gastroenterol Hepatol. 2007 Aug;4(8):426-7. Epub 2007 Jul 10. No abstract available.
PMID: 17622226 [PubMed]

10:
Related Articles, Links
Kucera S, Isenberg G, Chak A, Wong RC, Das A, Faulx AL, Sivak MV Jr.

Postprocedure radiologist's interpretation of ERCP x-ray films: a prospective outcomes study.
Gastrointest Endosc. 2007 Jul;66(1):79-83.
PMID: 17591478 [PubMed - indexed for MEDLINE]

11:
Related Articles, Links
Ochs-Balcom HM, Falk G, Grady WM, Kinnard M, Willis J, Elston R, Eng C, Chak A.

Consortium approach to identifying genes for Barrett's esophagus and esophageal adenocarcinoma.
Transl Res. 2007 Jul;150(1):3-17. Epub 2007 May 25. Review.
PMID: 17585859 [PubMed - indexed for MEDLINE]

12:
Related Articles, Links
Thomas M, Howell DA, Carr-Locke D, Mel Wilcox C, Chak A, Raijman I, Watkins JL, Schmalz MJ, Geenen JE, Catalano MF.

Mechanical lithotripsy of pancreatic and biliary stones: complications and available treatment options collected from expert centers.
Am J Gastroenterol. 2007 Sep;102(9):1896-902. Epub 2007 Jun 15.
PMID: 17573790 [PubMed - indexed for MEDLINE]

13:
Related Articles, Links
Chak A.

Endoscopy to endocytoscopy to endopathology: are we ready?
Endoscopy. 2007 Jun;39(6):540-1. No abstract available.
PMID: 17554651 [PubMed - indexed for MEDLINE]

14:

Related Articles, Links

Topazian M, Enders F, Kimmey M, Brand R, Chak A, Clain J, Cunningham J, Eloubeidi M, Gerdes H, Gress F, Jagannath S, Kantsevoy S, LeBlanc JK, Levy M, Lightdale C, Romagnuolo J, Saltzman JR, Savides T, Wiersema M, Woodward T, Petersen G, Canto M.

Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds.
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PMID: 17382940 [PubMed - indexed for MEDLINE]

15:

Related Articles, Links

Onders RP, McGee MF, Marks J, Chak A, Rosen MJ, Ignagni A, Faulx A, Schomisch S, Ponsky J.

Natural orifice transluminal endoscopic surgery (NOTES) as a diagnostic tool in the intensive care unit.
Surg Endosc. 2007 Apr;21(4):681-3. Epub 2007 Feb 16.
PMID: 17364154 [PubMed - indexed for MEDLINE]

16:

Related Articles, Links

Das A, Singh P, Sivak MV Jr, Chak A.

Pancreatic-stent placement for prevention of post-ERCP pancreatitis: a cost-effectiveness analysis.
Gastrointest Endosc. 2007 Jun;65(7):960-8. Epub 2007 Feb 28.
PMID: 17331513 [PubMed - indexed for MEDLINE]

17:

Related Articles, Links

Wong RC, Farooq FT, Chak A.

Endoscopic Doppler US probe for the diagnosis of gastric varices (with videos).
Gastrointest Endosc. 2007 Mar;65(3):491-6.
PMID: 17321253 [PubMed - indexed for MEDLINE]

18:

Related Articles, Links

McGee MF, Rosen MJ, Marks J, Chak A, Onders R, Faulx A, Ignagni A, Schomisch S, Ponsky J.

A reliable method for monitoring intraabdominal pressure during natural orifice translumenal endoscopic surgery.

Surg Endosc. 2007 Apr;21(4):672-6. Epub 2007 Feb 7.
PMID: 17285385 [PubMed - indexed for MEDLINE]

19:

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Rieder F, Cheng L, Harnett KM, Chak A, Cooper GS, Isenberg G, Ray M, Katz JA, Catanzaro A, O'Shea R, Post AB, Wong R, Sivak MV, McCormick T, Phillips M, West GA, Willis JE, Biancani P, Fiocchi C.

Gastroesophageal reflux disease-associated esophagitis induces endogenous cytokine production leading to motor abnormalities.
Gastroenterology. 2007 Jan;132(1):154-65. Epub 2006 Oct 12.
PMID: 17241868 [PubMed - indexed for MEDLINE]

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Related Articles, Links
Onders R, McGee MF, Marks J, Chak A, Schilz R, Rosen MJ, Ignagni A, Faulx A, Elmo MJ, Schomisch S, Ponsky J.

Diaphragm pacing with natural orifice transluminal endoscopic surgery: potential for difficult-to-wean intensive care unit patients.
Surg Endosc. 2007 Mar;21(3):475-9. Epub 2006 Dec 20.
PMID: 17177078 [PubMed - indexed for MEDLINE]

21:

Related Articles, Links
Isenberg G, Chak A.

Should there be light in the esophageal tunnel? An appraisal of optical coherence tomography in Barrett's esophagus.
Gastrointest Endosc. 2007 Jan;65(1):57-9. Epub 2006 Sep 20. No abstract available.
PMID: 17137853 [PubMed - indexed for MEDLINE]

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Related Articles, Links
Boolchand V, Olds G, Singh J, Singh P, Chak A, Cooper GS.

Colorectal screening after polypectomy: a national survey study of primary care physicians.
Ann Intern Med. 2006 Nov 7;145(9):654-9. Summary for patients in: Ann Intern Med. 2006 Nov 7;145(9):I26.
PMID: 17088578 [PubMed - indexed for MEDLINE]

23:

Related Articles, Links
Chak A, Faulx A, Eng C, Grady W, Kinnard M, Ochs-Balcom H, Falk G.

Gastroesophageal reflux symptoms in patients with adenocarcinoma of the esophagus or cardia.
Cancer. 2006 Nov 1;107(9):2160-6.
PMID: 17019737 [PubMed - indexed for MEDLINE]

24:
Related Articles, Links
McGee MF, Rosen MJ, Marks J, Onders RP, Chak A, Faulx A, Chen VK, Ponsky J.

A primer on natural orifice transluminal endoscopic surgery: building a new paradigm.
Surg Innov. 2006 Jun;13(2):86-93. Review.
PMID: 17012148 [PubMed - indexed for MEDLINE]

25:
Related Articles, Links
Chak A, Ochs-Balcom H, Falk G, Grady WM, Kinnard M, Willis JE, Elston R, Eng C.

Familiality in Barrett's esophagus, adenocarcinoma of the esophagus, and adenocarcinoma of the gastroesophageal junction.
Cancer Epidemiol Biomarkers Prev. 2006 Sep;15(9):1668-73.
PMID: 16985029 [PubMed - indexed for MEDLINE]

26:
Related Articles, Links
Chak A, Rothstein RI.

Sedationless upper endoscopy.
Rev Gastroenterol Disord. 2006;6 Suppl 1:S3-11. Review.
PMID: 16957661 [PubMed - indexed for MEDLINE]

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Related Articles, Links
Das A, Chak A.

Reassessment of patients with esophageal cancer after neoadjuvant therapy.
Endoscopy. 2006 Jun;38 Suppl 1:S13-7. Review. No abstract available.
PMID: 16802216 [PubMed - indexed for MEDLINE]

28:
Related Articles, Links
Das A, Chak A, Cooper GS.

Temporal trend in relative risk of second primary colorectal cancer.
Am J Gastroenterol. 2006 Jun;101(6):1342-7.
PMID: 16771959 [PubMed - indexed for MEDLINE]

29:

Related Articles, Links
Das A, Thomas S, Zablotska LB, Neugut AI, Chak A.

Association of esophageal adenocarcinoma with other subsequent primary cancers.
J Clin Gastroenterol. 2006 May-Jun;40(5):405-11.
PMID: 16721221 [PubMed - indexed for MEDLINE]

30:

Related Articles, Links
Das A, Chak A, Sivak MV Jr, Payes J, Cooper GS.

Endoscopic ultrasonography and prognosis of esophageal cancer.
Clin Gastroenterol Hepatol. 2006 Jun;4(6):695-700. Epub 2006 May 19.
PMID: 16713744 [PubMed - indexed for MEDLINE]

31:

Related Articles, Links
Jacobson BC, Chak A, Hoffman B, Baron TH, Cohen J, Deal SE, Mergener K, Petersen BT, Petrini JL, Safdi MA, Faigel DO, Pike IM; ASGE/ACG Taskforce on Quality in Endoscopy.

Quality indicators for endoscopic ultrasonography.
Am J Gastroenterol. 2006 Apr;101(4):898-901. No abstract available.
PMID: 16635234 [PubMed - indexed for MEDLINE]

32:

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Sahai AV, Schembre D, Stevens PD, Chak A, Isenberg G, Lightdale CJ, Sivak MV Jr, Hawes RH.

A multicenter U.S. experience with EUS-guided fine-needle aspiration using the Olympus GF-UM30P echoendoscope: safety and effectiveness.
Gastrointest Endosc. 1999 Dec;50(6):792-6.
PMID: 10570338 [PubMed - indexed for MEDLINE]

114:
Related Articles, Links
Charles RJ, Chak A, Cooper GS, Wong RC, Sivak MV Jr.

Use of open access in GI endoscopy at an academic medical center.
Gastrointest Endosc. 1999 Oct;50(4):480-5.
PMID: 10502167 [PubMed - indexed for MEDLINE]

115:
Related Articles, Links

Chak A, Cooper GS.

Procedure-specific outcomes assessment for endoscopic ultrasonography.
Gastrointest Endosc Clin N Am. 1999 Oct;9(4):649-56, vii. Review.
PMID: 10495229 [PubMed - indexed for MEDLINE]

116:

Related Articles, Links
Catalano MF, Alcocer E, Chak A, Nguyen CC, Raijman I, Geenen JE, Lahoti S, Sivak MV Jr.

Evaluation of metastatic celiac axis lymph nodes in patients with esophageal carcinoma: accuracy of EUS.
Gastrointest Endosc. 1999 Sep;50(3):352-6.
PMID: 10462655 [PubMed - indexed for MEDLINE]

117:

Related Articles, Links
Soweid AM, Chak A, Katz JA, Sivak MV Jr.

Catheter probe assisted endoluminal US in inflammatory bowel disease.
Gastrointest Endosc. 1999 Jul;50(1):41-6.
PMID: 10385720 [PubMed - indexed for MEDLINE]

118:

Related Articles, Links
Chak A.

How far have we come with ultrasound miniprobes?
Endoscopy. 1999 May;31(4):329-32. No abstract available.
PMID: 10376463 [PubMed - indexed for MEDLINE]

119:

Related Articles, Links
Chak A, Isenberg G, Mallery S, Van Dam J, Cooper GS, Sivak MV Jr.

Prospective comparative evaluation of video US endoscope.
Gastrointest Endosc. 1999 Jun;49(6):695-9.
PMID: 10343211 [PubMed - indexed for MEDLINE]

120:

Related Articles, Links
Rex DK, Chak A, Vasudeva R, Gross T, Lieberman D, Bhattacharya I, Sack E, Wiersema M, Farraye F, Wallace M, Barrido D, Cravens E, Zeabart L, Bjorkman D, Lemmel T, Buckley S.

Prospective determination of distal colon findings in average-risk patients with proximal colon cancer.
Gastrointest Endosc. 1999 Jun;49(6):727-30.
PMID: 10343217 [PubMed - indexed for MEDLINE]

121:
Related Articles, Links
Cooper GS, Yuan Z, Chak A, Rimm AA.

Geographic and patient variation among Medicare beneficiaries in the use of follow-up testing after surgery for nonmetastatic colorectal carcinoma.
Cancer. 1999 May 15;85(10):2124-31.
PMID: 10326689 [PubMed - indexed for MEDLINE]

122:
Related Articles, Links
Chak A, Hawes RH, Cooper GS, Hoffman B, Catalano MF, Wong RC, Herbener TE, Sivak MV Jr.

Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis.
Gastrointest Endosc. 1999 May;49(5):599-604.
PMID: 10228258 [PubMed - indexed for MEDLINE]

123:
Related Articles, Links
Cooper GS, Chak A, Way LE, Hammar PJ, Harper DL, Rosenthal GE.

Early endoscopy in upper gastrointestinal hemorrhage: associations with recurrent bleeding, surgery, and length of hospital stay.
Gastrointest Endosc. 1999 Feb;49(2):145-52.
PMID: 9925690 [PubMed - indexed for MEDLINE]

124:
Related Articles, Links
Chak A, Soweid A, Hoffman B, Stevens P, Hawes RH, Lightdale CJ, Cooper GS, Canto MI, Sivak MV Jr.

Clinical implications of endoluminal ultrasonography using through-the-scope catheter probes.
Gastrointest Endosc. 1998 Nov;48(5):485-90.
PMID: 9831836 [PubMed - indexed for MEDLINE]

125:
Related Articles, Links

Cooper GS, Chak A, Way LE, Hammar PJ, Harper DL, Rosenthal GE.

Endoscopic practice for upper gastrointestinal hemorrhage: differences between major teaching and community-based hospitals.
Gastrointest Endosc. 1998 Oct;48(4):348-53.
PMID: 9786105 [PubMed - indexed for MEDLINE]

126:

Related Articles, Links

Chak A, Soweid A, Hoffman B, Stevens P, Hawes RH, Lightdale CJ, Cooper GS, Canto MI, Sivak MV Jr.

Clinical implications of catheter probe-assisted endoluminal ultrasonography.
Endoscopy. 1998 Aug;30 Suppl 1:A169-72. No abstract available.
PMID: 9765118 [PubMed - indexed for MEDLINE]

127:

Related Articles, Links

Chak A, Isenberg G, Mallery S, VanDam J, Cooper GS, Sivak MV Jr.

Video echoendoscopy in the United States.
Endoscopy. 1998 Aug;30 Suppl 1:A135-7. No abstract available.
PMID: 9765106 [PubMed - indexed for MEDLINE]

128:

Related Articles, Links

Isenberg G, Chak A, Canto MI, Levitan N, Clayman J, Pollack BJ, Sivak MV Jr.

Endoscopic ultrasound in restaging of esophageal cancer after neoadjuvant chemoradiation.
Gastrointest Endosc. 1998 Aug;48(2):158-63.
PMID: 9717781 [PubMed - indexed for MEDLINE]

129:

Related Articles, Links

Chak A.

Spearing pseudocysts with Seldinger and sonography.
Gastrointest Endosc. 1998 Aug;48(2):221-4. No abstract available.
PMID: 9717798 [PubMed - indexed for MEDLINE]

130:

Related Articles, Links

Canto MI, Chak A, Stellato T, Sivak MV Jr.

Endoscopic ultrasonography versus cholangiography for the diagnosis of choledocholithiasis.
Gastrointest Endosc. 1998 Jun;47(6):439-48.
PMID: 9647366 [PubMed - indexed for MEDLINE]

131:

Related Articles, Links
Aabakken L, Chak A.

Internet for endoscopists: surf or drown?
Gastrointest Endosc. 1998 May;47(5):423-5. No abstract available.
PMID: 9609444 [PubMed - indexed for MEDLINE]

132:

Related Articles, Links
Hornbuckle K, Chak A, Lazarus HM, Cooper GS, Kutteh LA, Gucalp R, Carlisle PS, Sparano J, Parker P, Salata RA.

Determination and validation of a predictive model for Clostridium difficile diarrhea in hospitalized oncology patients.
Ann Oncol. 1998 Mar;9(3):307-11.
PMID: 9602265 [PubMed - indexed for MEDLINE]

133:

Related Articles, Links
Cooper GS, Chak A, Connors AF Jr, Harper DL, Rosenthal GE.

The effectiveness of early endoscopy for upper gastrointestinal hemorrhage: a community-based analysis.
Med Care. 1998 Apr;36(4):462-74.
PMID: 9544587 [PubMed - indexed for MEDLINE]

134:

Related Articles, Links
Chak A, Cooper GS, Canto MI, Pollack BJ, Sivak MV Jr.

Enteroscopy for the initial evaluation of iron deficiency.
Gastrointest Endosc. 1998 Feb;47(2):144-8.
PMID: 9512279 [PubMed - indexed for MEDLINE]

135:

Related Articles, Links
Chak A, Koehler MK, Sundaram SN, Cooper GS, Canto MI, Sivak MV Jr.

Diagnostic and therapeutic impact of push enteroscopy: analysis of factors associated with positive findings.

Gastrointest Endosc. 1998 Jan;47(1):18-22.
PMID: 9468418 [PubMed - indexed for MEDLINE]

136:
Related Articles, Links
Chak A.

Endoscopic ultrasound-guided fine-needle aspiration: time to temper enthusiasm with caution.
Gastrointest Endosc. 1997 Sep;46(3):286. No abstract available.
PMID: 9378224 [PubMed - indexed for MEDLINE]

137:
Related Articles, Links
Cooper GS, Yuan Z, Rosenthal GE, Chak A, Rimm AA.

Lack of gender and racial differences in surgery and mortality in hospitalized Medicare beneficiaries with bleeding peptic ulcer.
J Gen Intern Med. 1997 Aug;12(8):485-90.
PMID: 9276654 [PubMed - indexed for MEDLINE]

138:
Related Articles, Links
Pollack BJ, Chak A, Dahman B, Sivak MV Jr.

Warfarin therapy complicated by recurrent hemobilia in a patient with sarcoidosis.
Gastrointest Endosc. 1997 Jul;46(1):72-6. No abstract available.
PMID: 9260711 [PubMed - indexed for MEDLINE]

139:
Related Articles, Links
Chak A, Canto MI, Rösch T, Dittler HJ, Hawes RH, Tio TL, Lightdale CJ, Boyce HW, Scheiman J, Carpenter SL, Van Dam J, Kochman ML, Sivak MV Jr.

Endosonographic differentiation of benign and malignant stromal cell tumors.
Gastrointest Endosc. 1997 Jun;45(6):468-73.
PMID: 9199902 [PubMed - indexed for MEDLINE]

140:
Related Articles, Links
Chak A, Canto M, Stevens PD, Lightdale CJ, Van de Mierop F, Cooper G, Pollack BJ, Sivak MV Jr.

Clinical applications of a new through-the-scope ultrasound probe: prospective comparison with an ultrasound endoscope.
Gastrointest Endosc. 1997 Mar;45(3):291-5. No abstract available.

PMID: 9087836 [PubMed - indexed for MEDLINE]

141:
Related Articles, Links
Chak A, Post AB, Cooper GS.

Clinical variables associated with colorectal cancer on colonoscopy: a prediction model.
Am J Gastroenterol. 1996 Dec;91(12):2483-8.
PMID: 8946970 [PubMed - indexed for MEDLINE]

142:
Related Articles, Links
Nickl NJ, Bhutani MS, Catalano M, Hoffman B, Hawes R, Chak A, Roubein LD, Kimmey M, Johnson M, Affronti J, Canto M, Sivak M, Boyce HW, Lightdale CJ, Stevens P, Schmitt C.

Clinical implications of endoscopic ultrasound: the American Endosonography Club Study.
Gastrointest Endosc. 1996 Oct;44(4):371-7.
PMID: 8905352 [PubMed - indexed for MEDLINE]

143:
Related Articles, Links
Koehler M, Chak A, Setrakian S, Sivak MV Jr.

Endoscopic appearance of Mycobacterium genavense: case report and review of the literature.
Gastrointest Endosc. 1996 Sep;44(3):331-3. No abstract available.
PMID: 8885356 [PubMed - indexed for MEDLINE]

144:
Related Articles, Links
Cooper GS, Chak A, Harper DL, Pine M, Rosenthal GE.

Care of patients with upper gastrointestinal hemorrhage in academic medical centers: a community-based comparison.
Gastroenterology. 1996 Aug;111(2):385-90.
PMID: 8690203 [PubMed - indexed for MEDLINE]

145:
Related Articles, Links
Chak A, Cooper GS, Blades EW, Canto M, Sivak MV Jr.

Prospective assessment of colonoscopic intubation skills in trainees.
Gastrointest Endosc. 1996 Jul;44(1):54-7.

PMID: 8836717 [PubMed - indexed for MEDLINE]

146:

Related Articles, Links

Canto MI, Setrakian S, Petras RE, Blades E, Chak A, Sivak MV Jr.

Methylene blue selectively stains intestinal metaplasia in Barrett's esophagus.
Gastrointest Endosc. 1996 Jul;44(1):1-7.
PMID: 8836709 [PubMed - indexed for MEDLINE]

147:

Related Articles, Links

Pollack BJ, Chak A, Sivak MV Jr.

Endoscopic ultrasonography.
Semin Oncol. 1996 Jun;23(3):336-46. Review.
PMID: 8658217 [PubMed - indexed for MEDLINE]

148:

Related Articles, Links

Chak A, Canto M, Gerdes H, Lightdale CJ, Hawes RH, Wiersema MJ, Kallimanis G, Tio TL, Rice TW, Boyce HW Jr, et al.

Prognosis of esophageal cancers preoperatively staged to be locally invasive (T4) by endoscopic ultrasound (EUS): a multicenter retrospective cohort study.
Gastrointest Endosc. 1995 Dec;42(6):501-6.
PMID: 8674918 [PubMed - indexed for MEDLINE]

149:

Related Articles, Links

Wiersema MJ, Chak A, Kopecky KK, Wiersema LM.

Duplex Doppler endosonography in the diagnosis of splenic vein, portal vein, and portosystemic shunt thrombosis.
Gastrointest Endosc. 1995 Jul;42(1):19-26.
PMID: 7557171 [PubMed - indexed for MEDLINE]

150:

Related Articles, Links

Chak A, Sivak MV.

Electronic endoscopy, blood flow measurement and autofluorescence tissue spectroscopy.
Endoscopy. 1994 Jan;26(1):169-74. Review. No abstract available.
PMID: 8205989 [PubMed - indexed for MEDLINE]

151:
Related Articles, Links
Wiersema MJ, Chak A, Wiersema LM.

Mediastinal histoplasmosis: evaluation with endosonography and endoscopic fine-needle aspiration biopsy.
Gastrointest Endosc. 1994 Jan-Feb;40(1):78-81. No abstract available.
PMID: 8163144 [PubMed - indexed for MEDLINE]

152:
Related Articles, Links
Chak A, Banwell JG.

Traveler's diarrhea.
Gastroenterol Clin North Am. 1993 Sep;22(3):549-61. Review.
PMID: 8406730 [PubMed - indexed for MEDLINE]

153:
Related Articles, Links
Wiersema MJ, Kochman ML, Chak A, Cramer HM, Kesler KA.

Real-time endoscopic ultrasound-guided fine-needle aspiration of a mediastinal lymph node.
Gastrointest Endosc. 1993 May-Jun;39(3):429-31. No abstract available.
PMID: 8390383 [PubMed - indexed for MEDLINE]

154:
Related Articles, Links
Chak A, Karlin A.

Purification and reconstitution of nicotinic acetylcholine receptor.
Methods Enzymol. 1992;207:546-55. No abstract available.
PMID: 1528124 [PubMed - indexed for MEDLINE]

155:
Related Articles, Links
Karlin A, DiPaola M, Kao P, Wang L, Czajkowski C, Chak A.

Functional sites of the nicotinic acetylcholine receptor.
P R Health Sci J. 1988 Aug;7(2):75. No abstract available.
PMID: 2847218 [PubMed - indexed for MEDLINE]

156:
Related Articles, Links
Chák A.

Insoluble zinc-precipitated phosphomonoesterase from rat kidney.
Experientia. 1977 Jan 15;33(1):16-7. No abstract available.
PMID: 188677 [PubMed - indexed for MEDLINE]

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Lin Chang, M.D.	Professor of Medicine
eRA COMMONS USER NAME	
changl2	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, Los Angeles, CA	B.S.	1978-1982	Biochemistry
UCLA School of Medicine	M.D.	1982-1986	Medicine
Harbor-UCLA Medical Center	M.D.	1986-1989	Internal Medicine
UCLA Affiliated GI Fellowship Training Program	M.D.	1989-1992	Gastroenterology

A. Positions and Honors.

Positions and Employment

1992 – 1993 Associate Consultant, Gastroenterology, Mayo Clinic, Rochester, MN
1993 – 1997 Assistant Professor of Medicine, UCLA School of Medicine, Department of Medicine, Div. of Gastroenterology, Harbor-UCLA Medical Center
1997 – 2000 Adjunct Assistant Professor of Medicine, UCLA School of Medicine, Div. of Digestive Diseases, UCLA
2000 – 2006 Associate Professor of Medicine, David Geffen School of Medicine at UCLA, Div. of Digestive Diseases. Co-Director, Center for Neurovisceral Sciences and Women's Health
2006 – Present Professor of Medicine-in-Residence, David Geffen School of Medicine at UCLA, Div. of Digestive Diseases. Co-Director, Center for Neurovisceral Sciences and Women's Health

Honors

1995 Auxiliary Award, American College of Gastroenterology
2002 Janssen Award in Gastroenterology, Basic or Clinical Research
2002 Women in Gastroenterology and Wyeth Award for Gender Based Research, ACG

B. Selected peer-reviewed publications (in chronological order).

1. Munakata J, Naliboff B, Harraf F, Kodner A, Lembo T, **Chang L,** Silverman DHS, Mayer EA. Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. Gastroenterology 1997;112:55-63.
2. Naliboff BD, Munakata J, **Chang L,** Mayer EA. Toward a biobehavioral model of visceral hypersensitivity in irritable bowel syndrome. J Psychosom Res 1998:45:485-492.
3. Schmulson M, Lee O, **Chang L,** Naliboff B, Mayer EA. Symptom differences in moderate to severe IBS patients based on predominant bowel habit. Am J Gastroenterol 1999:94:2929-2935.
4. Mayer EA, Naliboff B, Lee O, Munakata J, **Chang L.** Gender-related differences in functional gastrointestinal disorders. Aliment Pharmacol Ther 1999;13:65-69.
5. **Chang L,** Mayer EA, FitzGerald L, Stains J, Naliboff B. Differences in somatic perception in patients with irritable bowel syndrome with and without fibromyalgia. Pain 2000;84:297-307.
6. Schmulson M, **Chang L,** Naliboff B, Lee O, Mayer EA. Correlation of symptom criteria with perception thresholds during rectosigmoid distension in irritable bowel syndrome. Am J Gastroenterol 2000;95:152-156.
7. Lee OY, FitzGerald LZ, Naliboff B, Liu C, Schmulson M, Fullerton S, Mayer EA, **Chang L.** Impact of advertisement and clinic populations in symptoms and perception of irritable bowel syndrome. Aliment Pharmacol Ther 2000;13:1631-1638.

8. **Chang L**, Munakata J, Mayer EA, Schmulson MJ, Johnson TD, Bernstein CN, Saba L, Naliboff B, Anton PA, Matin K. Perceptual responses in patients with inflammatory and functional bowel disease. Gut 2000;47:497-505.
9. Berman S, Munakata J, Naliboff B, **Chang L**, Mandelkern MA, Silverman D, Kovalik E, Mayer EA. Gender differences in regional brain response to visceral pressure in IBS patients. Eur J Pain 2000;4:157-172.
10. Naliboff B, Derbyshire SWG, Munakata J, Berman S, Mandelkern M, **Chang L**, Mayer EA. Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation. Psychosom Med 2001;63:365-375.
11. Lee OY, Mayer EA, Schmulson M, **Chang L**, Naliboff B. Gender related differences in irritable bowel syndrome symptoms. Am J Gastroenterol 2001;96:2184-2193.
12. **Chang L**, Lee OY, Naliboff B, Schmulson M, Mayer EA. Bloating and abdominal distension symptoms in patients with irritable bowel syndrome. Am J Gastroenterol 2001;96:3341-3347.
13. Mayer EA, Naliboff BD, **Chang L**, Coutinho SV. Stress and irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2001;280:G519-524.
14. Berman SM, **Chang L**, Suyenobu B, Derbyshire SW, FitzGerald L, Mandelkern M, Hamm L, Vogt B, Naliboff BD, Mayer EA. Condition-specific deactivation of bran region by 5-HT_3 receptor antagonist alosetron. Gastroenterology 2002;123:969-977.
15. Sach J, Bolus R, Fitzgerald L, Naliboff BD, **Chang L**, Mayer EA. Is there a difference between abdominal pain and discomfort in moderate to severe IBS patients? Am J Gastroenterol 2002;97:3131-8.
16. Heitkemper M, Elta G, Carter EG, Ameen V, Olden KW, **Chang L**. Women with Irritable Bowel Syndrome: Differences in Patients' and Physicians' Perceptions. Gastroenterol Nurs 2002;25:192-200.
17. **Chang L**, Heitkemper MM. Gender Differences in Irritable Bowel Syndrome. Gastroenterology 2002;123:1686-1701.
18. Naliboff BD, Berman S, **Chang L**, Derbyshire SW, Suyenobu B, Vogt BA, Mandelkern M, Mayer EA. Sex-related differences in IBS patients:Central processing of visceral stimuli. Gastroenterol 2003;124:1738-47.
19. **Chang L**, Berman S, Mayer EA, Suyenobu B, Derbyshire S, Naliboff B, Vogt B, FitzGerald L, Mandelkern MA. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. Am J Gastroenterol 2003;98:1354-1361.
20. Schwetz I, Naliboff B, Munakata J, Lembo T, **Chang L**, Matin K, Ohning G, Mayer EA. Anti-hyperalgesic effect of octreotide in patients with irritable bowel syndrome. Aliment Pharmacol Ther 2004;19:123-131.
21. Spiegel BM, Gralnek IM, Bolus R, **Chang L**, Dulai GS, Mayer EA, Naliboff B. Clinical determinants of health-related quality of life in patients with irritable bowel syndrome. Arch Intern Med 2004;164:1773-1780.
22. Mayer EA, Berman S, **Chang L**, Naliboff BD. Sex-based differences in gastrointestinal pain. Eur J Pain 2004;8:451-463.
23. Mayer EA, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff B, **Chang L**. Brain responses to visceral pain between male patients with irritable bowel syndrome and ulcerative colitis. Pain 2005;115(3):398-409.
24. **Chang L**, Ameen VZ, Dukes G, McSorley DJ, Mayer EA. A dose-ranging, phase II study of the efficacy and safety of alosetron hydrochloride (Lotronex®) in men with diarrhea-predominant IBS. Am J Gastroenterol 2005;100:115-123.
25. Tillisch K, Labus JS, Naliboff BD, Bolus R, Shetzline M, Mayer EA, **Chang L**. Characterization of the alternating bowel habit subtype in patients with irritable bowel syndrome. Am J Gastroenterol 2005; 100(4):896-904
26. Dunckley P, Wise R, Painter D, Brooks J, Tracey I, Aziz Q, **Chang L**. Cortical processing of visceral and somatic stimulation - differentiating pain intensity from unpleasantness. Neurosci 133(2):533-42, 2005.
27. Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, **Chang L**, Tracey I. A comparison of visceral and somatic pain processing in the human brainstem using fMRI. J Neurosci 2005;25(32):7333-41.
28. Tillisch K, Mayer EA, Labus JS, Stains J, **Chang L**, Naliboff BD. Gender-specific alterations in autonomic function among patients with irritable bowel syndrome. Gut 2005;28: 54(10):1396-1401.
29. **Chang L**. Neuroendocrine and Neuroimmune Markers in IBS: Pathophysiological role or epiphenomenon? Gastroenterology 2006;130:596-600.
30. **Chang L**, Chey WD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: Systematic review of clinical trials and post-marketing surveillance data. **Am J Gastroenterol** 2006; 101(5):1069-79.

C. Research Support

Ongoing Research Support

R01 AR46122-01 Chang (PI) 07/01/99 – 01/31/11 55% effort
NIH
Neuroendocrine Alterations in Fibromyalgia and IBS
Initial grant: This study has the goal of comparing perceptual, neuroendocrine, autonomic, and CNS responses in irritable bowel syndrome (IBS) and fibromyalgia.
Renewal grant: This study assesses the role of enhanced pain amplification mechanisms of heightened attention and symptom-specific anxiety in IBS and fibromyalgia.
Role: PI

1P50 DK64539-01 Mayer (PI) 09/30/02 – 08/31/07 30% effort
NIH P50 Center Grant
Women's Center for Functional Visceral Disorders
Project 3: Sex differences in neuroendocrine and immunologic responses in IBS
The goals of this project are: 1) To identify if the basal levels of the central stress response systems, the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), differ in men and women with irritable bowel syndrome (IBS). 2) To determine stress-induced responsiveness of the HPA axis and SNS differ in men and women with IBS. 3) To determine if IBS patients have altered plasma and mucosal cytokine production during IBS symptom exacerbation and if these responses are associated with changes in HPA and SNS responsiveness and visceral sensitivity.
Role: PI – Proj. 3

M01-RR00865 Levey (PI) 12/01/01 – 11/30/06 10% effort
NIH/NCRR
General Clinical Research Center
The aim of this study is to participate in the general clinical research center for clinical research projects.
Role: Co-I

GlaxoSmithKline – Investigator-initiated Chang (PI) 11/01/03-12/31/07 5% effort
Study # RA03-18
Colonic mucosal immune markers in IBS
The aims of this study are to determine in colonic mucosal tissue specimens taken from IBS patients, compared to controls: 1) the number of colonic tissue enterochromaffin cells, lymphocytes and mast cells 2) gene microarray analysis for cytokines in colonic mucosal tissue, and 3) distribution of a variety of neurotransmitters, receptors, ion channels, and enzymes in the colonic mucosal tissue samples including peptides and receptors of the CRF system, calcium activated potassium channels (SK and IK channels), receptors for 5-HT, and receptors of the PAR family, and levels of iNOS.
Role: PI

Completed Research Support

14278 Mayer (PI) 01/01/97 – 06/30/03
AstraZeneca
Basic and Clinical Studies in Functional GI Disorders
The major goals of this program are to develop new pharmacological treatments for functional digestive diseases. Specific research projects address: 1) development of techniques for visceral sensitivity testing in rats, mice and humans; 2) examination of potential treatment compounds in animal models; 3) cellular and molecular mechanisms of visceral sensation; and 4) human trials.
Role: Co-Investigator

R01 NR04881 Naliboff (PI) 07/01/98 – 06/30/01
NIH

Gender Related Differences in Visceral Sensitivity in IBS
The major goals of this project are: 1) Compare symptoms, visceral sensitivity and regional brain activation using PET in male and female patients with IBS; 2) Compare symptoms, visceral sensitivity and regional brain activation in female patients with IBS at two time points during their menstrual cycle.
Role: Co-Investigator

GlaxoWellcome Investigator Initiated Chang (PI) 09/01/00 – 12/31/01
A Pilot Study to Assess Nocturnal Autonomic Arousal in Female Subjects with Diarrhea-Predominant Irritable Bowel Syndrome as Compared with Healthy Controls
The aim of this study is to compare sleep patterns, autonomic and neuroendocrine responses, and colonic motility in female subjects with IBS and healthy controls.
Role: PI

Novartis Investigator Initiated Chang (PI) 07/01/03 – 06/30/05
Characterization of Irritable Bowel Syndrome with Alternating Bowel Habits
The aim of this study is to characterize symptoms in the IBS subgroup with alternating bowel habits and to compare symptom severity, extraintestinal and psychological symptoms and health related quality of life with the other two IBS subgroups with diarrhea predominance and constipation predominance.
Role: PI

R01 DK48351 Mayer (PI) 07/01/01 – 05/31/06
NIH
Perception and Modulation of Visceral Sensations
The major goals of this project are: 1) Compare rectal sensitivity in patients with IBS, inflammatory bowel disease and controls; 2) Compare rectal and esophageal sensitivity in IBS patients; 3) Using PET imaging, examine the brain regions associated with rectal and esophageal stimulation in patients with IBS, inflammatory bowel disease, and controls; 4) Examine opioid mechanisms of visceral sensitivity using naloxone challenge.
Role: Co-Investigator

Linda E. Greenbaum, M.D.

Assistant Professor of Medicine

Department: **Medicine**

Graduate Group Affiliations
- Cell and Molecular Biology
- Pharmacological Sciences

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GREENBAL@MAIL.MED.UPENN.EDU

Links
Search PubMed for articles
Cell and Molecular Biology graduate group faculty webpage.
Pharmacological Science graduate group faculty webpage.

Education
B.A. (Biology)
Harvard University, 1980.

M.D.
Columbia University, 1984.

Permanent link

Description of Research Expertise

Research Interests
cell proliferation, differentiation and injury in the mammalian liver

Key words: liver, cell cycle, apoptosis, cancer.

Description of Research
The main goal of the Greenbaum lab is to understand the molecular mechanisms that govern cell proliferation, differentiation and mechanisms of injury and repair in the mammalian liver. These processes are of vital importance to human health given the recent rise in hepatocellular carcinoma.

We are investigating the molecular pathways responsible for hepatocyte growth and proliferation using the partial hepatectomy model in mouse models. Understanding the mechanisms that regulate the cell cycle in normal hepatocytes in response to growth, injury and metabolic signals will be applicable to understanding abnormal regulation of these pathways in hepatocellular carcinoma and in patients with inadequate liver recovery associated with fulminant liver failure. In addition to standard molecular analyses, we also utilize high throughput genomics and computational approaches.

1. Regulation of DNA replication licensing proteins by C/EBPβ

Proliferation in the liver, which is normally characterized by very low cell turnover, can be dramatically stimulated in the partial hepatectomy model. After surgical removal of 2/3 of the liver, the remaining hepatocytes exit G0 and synchronously enter the cell cycle in order to restore liver mass. We have investigated the role of the E2F transcription factors during this process, as these factors have been shown to control the expression of a large number of genes involved in DNA replication and cell cycle progression. Liver cell proliferation after partial hepatectomy is one of the best mammalian in vivo models of synchronized exit from G0 and entry into the cell cycle. One of the fundamental questions in the field of cell cycle regulation is "How is biological specificity within the E2F family achieved?" The bZIP transcription factor CCAAT enhancer binding protein beta (C/EBPβ) is phosphorylated in response to activation of metabolic, cytokine and growth factor pathways linked to cell growth, making it a likely candidate for participating in the regulation of cell cycle associated genes in the liver. We have identified a group of E2F-regulated genes including several that are involved in licensing origins of replication that are markedly reduced in C/EBPβnull mice. These findings identify C/EBPβ as a direct activator of E2F promoters and cell cycle progression in the mammalian cell cycle. We have recently established that C/EBPβ and E2Fs synergistically activate the promoter of one of these licensing proteins, CDC6. Current studies are focused on defining the mechanism through which this synergistic activation occurs and are investigating the contribution of posttranslational modifications to the C/EBPβ protein downstream of various signaling pathways that modulate C/EBPβ activation of cell cycle gene expression and hepatocyte proliferation.

2. Coactivator protein regulation of liver regeneration
Transcriptional coactivator proteins are recruited to target gene promoters in response to cellular signals and mediate the adaptation to changes in tissue homeostasis. We have recently made the novel observation that the PGC-1alpha coactivator, a critical molecule for gluconeogenesis during fasting, is dramatically induced in the regenerating liver. Current studies are focused on identification of the signaling pathways that regulate its expression and function during liver regeneration.

3. MicroRNA regulation of hepatocyte proliferation
MicroRNAs are small noncoding RNA molecules that inhibit gene expression via degradation of target mRNAs, inhibition of protein translation or chromatin silencing. These molecules have been implicated in a variety of cellular functions including proliferation, apoptosis and metabolism and dysregulation of these molecules has been linked to carcinogenesis. We are currently investigating the contribution of microRNAs to hepatocyte proliferation in the regenerating liver.

Rotation Projects for 2007-2008: (subject to change)

Analysis of the mechanism of E2F target gene regulation by C/EBPβ.
1. Identification of C/EBPβ protein domains that mediate binding to E2F proteins and effect synergistic activation of cell cycle genes using mutagenesis and co-immunoprecipitation.
2. Analysis of signaling pathways that contribute to C/EBPβ regulation of hepatocyte proliferation. Construction of adenoviral vectors expressing mutated C/EBPβ molecules will be assessed for their ability to rescue proliferation and E2F target gene expression in primary mouse hepatocytes.

Investigation of microRNAs for hepatocyte proliferation
Northern blot analysis will be used to identify differentially expressed microRNAs in the regenerating liver. Antisense constructs targeted to candidate microRNAs will be injected via tail vein to determine the function of these microRNAs during liver regeneration.

Lab personnel:
Yan Gao, Postdoctoral researcher
Jenny Yan, Research Specialist
Akivaga Tsingalia, Research Specialist
Sarah Muse, Graduate student in the CAMB program

Selected Publications

Wang, H., Larris, B., Peiris, T.H., Zhang, L., Le Lay, J., Gao, Y., Greenbaum, L.E.: *C/EBPbeta activates E2F-regulated genes in vivo via recruitment of the coactivator CREB-binding protein/p300*. Journal of Biological Chemistry 282(34): 24679-88, August 2007 Notes: Epub 2007, June 27.

Zhang, L., Rubins, N.E., Ahima, R.S., Greenbaum, L.E., and K.H. Kaestner. : *Foxa2 integrates the transcription response of the hepatocyte to fasting*. Cell Metabolism 2: 141-8, 2005.

White, P, Brestelli, J.E., Kaestner, K.H. and L.E. Greenbaum: *Identification of transcriptional networks during liver regeneration*. J. Biol. Chem 280: 3715-3722, 2005.

Greenbaum, L.E.: *Cell Cycle Regulation and Hepatocarcinogenesis*. Cancer Biology and Therapy 3: 1200-1207, Dec 2004.

Friedman, J.R., Larris, B., Le, P.P., Peiris, T.H., Arsenlis, A., Schug, J., Tobias, J.W., Kaestner, K.H., and L.E. Greenbaum: *Orthogonal analysis of C/ EBPbeta targest in vivo during liver proliferation*. Proc. Natl. Acad. Sci., USA 101: 12986-12991, 2004.

Debonera, F., Aldeguer, X., Shen, X., Gelman, A.E., Que, X., Greenbaum, L. E., Further, E.E., Taub, R., and K.M. Olthoff.: *Activation of IL-6/STAT3 and liver regeneration following transplantation*. Journal of Surgical Research 96: 289-295, 2001.

Mukherjee, D., Kaestner, K. H., ..and L. E. Greenbaum.: *Fas-induced apoptosis in murine hepatocytes is dependent on C/EBPâ*. Hepatology 33: 1166-72, 2001.

Kovalovich, K., Li, DeAngelis, R., Greenbaum, L.E., Ciliberto, G., and R. Taub.: *IL-6 protects against Fas-mediated death by establishing a critical level of anti-apoptotic hepatic proteins FLIP, Bcl-2 and Bcl-xL*. J. Biol. Chem. 276: 26605-26613, 2001.

Greenbaum, L., Kovalovich, K., Taub, R., Ciliberto, G., Poli, V.: *CCAAT enhancer binding protein beta is required for Fas-induced apoptosis in liver*. Gastroenterology. 118(4): 982, Apr 2000 Notes: Part 1, Suppl. 2.

Greenbaum, L., Li, W., Peng, Y., Ciliberto, G., Poli, V.: *Impaired hepatocyte DNA synthesis in CCAAT enhancer binding protein â mice is associated with dysregulation of members of the retinoblastoma and E2F family of transcription factors*. Hepatology Nov 1999 Notes: Suppl.

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Last updated: 10/04/2007

Peter J. Harvison, Ph.D.

Faculty:
Analytical Chemistry
Biochemistry
Chemical Education
Computational Chemistry
Inorganic Chemistry
Medicinal Chemistry
Natural Products Chemistry
Organic Chemistry
Pharmaceutical Chemistry
Physical Chemistry
Staff Listing
Faculty Listing

Resources
Awards
Career Opportunities
Course Descriptions
Current Courses
Curricula
Employment Opportunities
Facilities
Faculty-Staff
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Peter J. Harvison
Research Associate Professor of Medicinal Chemistry
Associate Professor, Pharmaceutical Sciences
Ph.D., Medicinal Chemistry
SUNY Buffalo, 1983

Medicinal Chemistry

Biochemistry

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Research Interests

- Drug metabolism
- HPLC method development
- Structure activity/toxicity relationships

Research Summary

My research interests are primarily concerned with the effects of metabolism on the biological activity of chemicals (including drugs) to which humans and other mammals may be exposed. Although metabolism usually results in the formation of nontoxic substances, the opposite can also occur. For example, some chemicals are actually converted into highly toxic metabolites that can damage tissues or cause cancer.

In particular, my research has focused on a compound known as (3,5-dichlorophenyl)succinimide (NDPS), that was originally developed as an agricultural fungicide. Although NDPS is an effective antifungal agent, it is converted into metabolites that can produce severe kidney damage in laboratory rats. In fact, NDPS has never been used commercially due to concerns about its potential

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toxicity in humans. However, humans are exposed to compounds that are structurally related to NDPS. Therefore, a goal of my research efforts is to determine why NDPS is toxic. We use a variety of techniques, including high performance liquid chromatography (HPLC) and mass spectrometry, to investigate NDPS metabolism. These results of these studies may help us understand why NDPS and other chemicals can produce kidney damage in animals and humans.

Recent or Representative Publications

‡ Undergraduate Student
* Graduate Student

C.M. Henesey and P.J. Harvison, 2002, "Renal Damage, Metabolism and Covalent Binding Following Administration of the Nephrotoxicant N-(3,5-Dichlorophenyl)succinimide (NDPS) to Male Fischer 344 Rats" Toxicology 170, 187-200. D.Cui and P.J. Harvison, 2000, "Determination of the Site of Glucuronidation in an N-(3,5-Dichlorophenyl) succinimide Metabolite by Electrospray Tandem Mass Spectrometry Following Derivatization to Picolinyl Esters," Rapid Commun. Mass Spectrom. 14, 1985-1990

C.M. Henesey*, G.L. Kellner-Weibel*, J.B. Tarloff, and P.J. Harvison, 1999, "Comparative disposition of the nephrotoxicant N-(3,5-dichlorophenyl)succinimide and the non-nephrotoxicant N-(3,5-difluorophenyl)succinimide in Fischer 344 rats" Drug. Metab. Dispos. 27, 674-680.

R.J. Griffin* and P.J. Harvison, 1998, "In vivo metabolism and disposition of the nephrotoxicant N-(3,5-dichlorophenyl)succinimide in Fischer 344 rats," Drug Metab. Dispos., 26, 907-913.

G.L. Kellner-Weibel*, R. Tchao, C.M. Henesey*, A.K. Nyarko*, and P.J. Harvison, 1997, "The effect of aromatic fluorine substitution on the nephrotoxicity and metabolism of N-(3,5-dichlorophenyl)succinimide in Fischer 344 rats," Toxicology, 117, 73-83.

A.K. Nyarko*, G.L. Kellner-Weibel*, and P.J. Harvison, 1997, "Cytochrome P450-mediated metabolism and nephrotoxicity of N-(3,5-dichlorophenyl)succinimide in rats," Fundam. Appl. Toxicol., 37, 117-124.

John Thomas Lamont, M.D.: Dr. Lamont is chief of the division of gastroenterology at Beth Israel Deaconess Medical Center and a professor of medicine at the Boston University of Rochester. Dr. Lamont interned at the UCLA Medical Center in Los Angeles, where he later served as chief medical resident.
He has been on the faculty of Boston University since 1980 and is certified in internal medicine and gastroenterology. Dr. Lamont's research interests include the structure and function of intestinal mucin and the mechanisms of action of bacterial toxins.

CURRICULUM VITAE AND BIBLIOGRAPHY

DATE:10/30/02

NAME: Gene David LeSage, M.D.

PRESENT TITLE: Professor of Medicine
Director of Division of Gastroenterology, Hepatology and Nutrition
Department of Medicine
The University of Texas at Houston Medical School

ADDRESS: 6431 Fannin, MSB 4.234
Houston, TX 770030

BIRTHDATE: February 19, 1953

CITIZENSHIP: United States of America

UNDERGRADUATE EDUCATION:

1968 - 1971	H.S. Diploma	Center High School Kansas City, Missouri
1971 – 1977	M.D., B.S.	University of Missouri at Kansas City Six year combined undergraduate and MD program

POSTGRADUATE TRAINING:

1977-1980	Residency Internal Medicine Mayo Clinic Rochester, Minnesota
1980	Fellow, Division of Gastroenterology Mayo graduate School of Medicine Rochester, MN. (E. Dickson, Program Director)
1980	Research Trainee Gastroenterology Unit Mayo Graduate School of Medicine (N. F. LaRusso, M. D., Advisor)
1981	Postdoctoral Research Fellowship of American Liver Foundation Gastroenterology Unit Mayo Graduate School of Medicine Rochester, MN. (N. F. LaRusso, M. D., Research Director)

1981-1982	Research Trainee The National Institutes of Health Gastroenterology Unit Mayo Graduate School of Medicine Rochester, MN. (N. F. LaRusso, M. D., Advisor)

ACADEMIC APPOINTMENTS:

1984-1992	Assistant Professor of Medicine Texas A&M University College of Medicine Scott and White Memorial Hospital Temple, Texas
1992 - 2002	Associate Professor of Medicine and of Medical Biochemistry and Genetics Texas A&M University Health Science Center Scott and White Memorial Hospital Temple, Texas
1985 – 2002	Member of the Center for the Study of Cell Surfaces Texas A&M University College of Medicine
1989 - 2002	Clinician Scientist Scott and White Memorial Hospital Texas A&M University College of Medicine
2002 – Present	Professor of Medicine The University of Texas at Houston Medical School Department of Internal Medicine Division of Gastroenterology, Hepatology and Nutrition
2002 – Present	Director Division of Gastroenterology, Hepatology and Nutrition The University of Texas at Houston Medical School Department of Medicine
2002 – Present	Chief Memorial Hermann Hospital Gastroenterology Division

HOSPITAL APPOINTMENTS:

2002 – Present	Memorial Hermann Hospital Houston, TX
2002 – Present	LBJ Harris County Hospital Houston, TX

LICENSURE:

1977	MD
1978	Diplomat of the National Board of Examiners
1980	Board certified Internal Medicine
1984	Board certified Gastroenterology
1984	State of Texas, No. G6201

CERTIFICATION:

1977	BA in biology and chemistry with distinction

PROFESSIONAL ORGANIZATIONS:

LOCAL:

2002	GI Research Forum
2002	Harris County Medical Society

REGIONAL:

1983	Texas Medical Association

NATIONAL:

1977	American Medical Association
1980	American Gastroenterological Association
1984	American Association for the Study of Liver Diseases
1986	American Physiological Society

HONORS AND AWARDS:

1969	National Honor Society
1972	University Scholar University of Missouri at Kansas City
1977	Phi Kappa Phi
1982	American Liver Foundation Scholarship
1994	Temple Campus Development for Establishment of Basic Research Center for Hepatic Diseases

EDITORIAL POSITIONS:

Hepatology

Gastroenterology

Journal of Clinical Investigation

Journal of Hepatology

American Journal of Physiology

PNAS

American Journal of Pathology

Laboratory Investigation

Digestive Diseases and Sciences

American Journal of Gastroenterology

Reviewer for AASLD and AGA abstracts

2000 Cell Biology Section
2001 Cell Biology Section

SERVICE ON NATIONAL GRANT REVIEW PANELS, STUDY SECTIONS, COMMITTEES:

Reviewer for the National Institutes of Health

1993 GMA-2 (ad-hoc reviewer)
1994 Ad-hoc study section – Immunlogical Sciences Study Section
2000 Virology Study Section (ad-hoc reviewer)
2001 NIH SBIR study section (June)
2001 NIH SBIR study section (Oct)
2002 NIH SBIR study section (Feb)
2002 NIH SBIR study section (Oct)

SERVICE ON GRADUATE SCHOOL COMMITTEES:

Medical School Curriculum (Texas A & M):

1984-1996 Second Year Introduction to Medicine, Liver Diseases Section

1996-2001	Second Year Introduction to Medicine, both Gastroenterology and Liver Diseases Sections
1987-1990	Biochemistry first year. Metal metabolism
1991-1996	Physiology first year. Changes in splanchnic circulation and renal function in liver disease
1998	Physiology first year. Changes in splanchnic circulation and renal function in liver disease
2001-2002	Course co-director for Gastroenterology block

Graduate School Curriculum (Texas A & M):

1996-2002	Member of Graduate Faculty Texas A&M University
1999-2002	Member of Graduate Faculty of the Texas A&M University System Health Sciences Center Graduate School of Biomedical Sciences

DOCTORAL THESIS COMMITTEES (Texas A & M):

S. Bateman	Nuclear Engineering
J. Boyson	Veterinary School
S. Falk	Biochemistry
B. Woo	Mathematics

COMMITTEES (Texas A & M):

1987-1990	Institutional Animal Care and Use Committee
1988-2000	Institutional Research Committee
1988-2002	Chairman of Long range planning committee (evaluation of potential change to Health Science Center and building new Medical Research Building in Temple), Texas A&M University College of Medicine
1993-2002	Internal Medicine representative on Facility Advisory Committee
1993-2002	Academic Council
1996	Chairman of Facility Advisory Committee
1995	Search Committee for Chairman of Anatomy Department
1997	LCME Subcommittee on Graduate Education in Basic Sciences
1998-99	Research Building Task Force Committee
1998 -99	M.D./Ph.D. Review committee
1998	Search Committee for Director of Research, College of Medicine
1999	Committee for design of space allocation policy, College of Medicine
2000-2002	Search Committee for the Dean of College of Medicine
2000-2002	Research Executive Committee, Texas A&M Health Science Center (The College of Medicine elected member)
2001–2002	Space committee, College of Medicine

SERVICE ON UT-HMS AFFILIATED HOSPITAL COMMITTEES:

Memorial Hermann Liver Transplant Medical Review Committee

Memorial Hermann Gastroenterology Service

SPONSORSHIP OF POSTDOCTORAL FELLOWS:

Name	Year	Title of Research Project
Mary Williams	1986	Biliary iron intestinal absorption in normal and iron Overloaded rats
Joseph Holland	1986	Treatment of fulminant hepatitis with hemofiltration
Douglas Kirkley	1987	Evaluation of the effect of atrial natriuretic peptide on bile flow in rats
Carlos Cardenas	1988	A new model for the study of portal and systemic hemodynamics in the laboratory rat.
M. Diaz	1988	Determination of microtubule morphology in hepatocytes employing fluorescence microscopy
J. Chapek	1987	Bile acid-dependent secretion of lysosomal enzymes into rat bile
Kelly Kensing	1989	The effects of age and sex on hepatic lidocaine metabolism.
Ivan Elias	1991	Antiproliferative effects of alpha-interferon in carbon tetrachloride (CCl_4)-induced cirrhosis.
Myers, John.	1992	Identification and characterization of intracellular membrane-associated organic anion binding sites in rat hepatocytes
Dominguez, A	1993	Organic and inorganic anion uptake into microsomal vesicles coupled to the vacuolar H^+ATPase
Sidawar Gubba	1994	Bile duct regrowth following partial hepatectomy
Dan Stagg	1995	Phenytoin-induced vanishing bile duct syndrome
Alessandra Caligiuri	1996-97	Endothelin-1 regulation ductal bile secretion.
Ziga Tretjak	1997	Carbon tetrachloride-induced bile duct injury
Emanuela Papa	1997	Carbon tetrachloride-induced bile duct injury

Leonardio Baiocchi	1998	Taurohyodeoxycholic acid and tauroursodeoxycholic acid have different mechanisms for bile acid-dependent hypercholeresis
Aline Ghaleb	1998	Cost-Of-Illness for Hepatitis C Patients
Noriatsu Kanno	1999-01	Bile acid regulation of cholangiocarcinoma growth.

CURRENT TEACHING RESPONSIBILITIES:

Attending Physician, Gastroenterology Service, Memorial Hermann Hospital

Attending Physician, Liver Transplant Service, Memorial Hermann Hospital

Attending Physician, Digestive Disease Center, Memorial Hermann Hospital

CURRENT GRANT SUPPORT:

2000-2005	NIDDK RO1 DK 54208 Principle Investigator (40% effort) "Bile acid regulation of bile duct secretion and proliferation" $1,151,500 (direct and indirect costs)
2002-2005	NIDDK RO1 DK 58411 Co-Investigator (15% effort) "Growth regulation of the intrahepaticbiliary tree" $ 703,222
2000-2004	VA Merit Award Co-investigator (5% effort) "Mechanisms of Cholangiocyte Proliferative and Secretory Heterogeneity" $750,000.
2001-2006	NIDDK RO1 Principle Investigator "Morphogenesis of Bile Ducts", (30% effort), Pending

PAST GRANT SUPPORT:

1994-2000	Project orientated Research Award, Scott and White Memorial Hospital, $960,000
1994-1997	Temple Campus Development Award for establishment of Center for Hepatic Diseases, Texas A&M University College of Medicine, $450,000
1989-1994	Clinician Scientist Award $825,000

PUBLICATIONS:

ABSTRACTS: (* - poster presentation, ** - oral presentation)

1) LeSage GD, Baldus WO, Fairbanks UF, Baggenstoss AH, McCall JT, Moore BS Taswell HF and Gordon H: Do all patients with heavy hepatic iron deposition have genetic hemochromatosis? Hepatology 1981;1:527. **

2) LeSage GD and LaRusso NF: Identification and partial characterization of an endogenous inhibitor of lysosomal enzymes in bile. Gastroenterology 1982;82:1234.*

3) LeSage GD, Kost LJ, McCall JT, Barham SS, Zinsmeister AR and LaRusso NF: Biliary excretion of iron from hepatocyte lysosomes: A novel excretory pathway in hepatic iron overload. Gastroenterology 1983;84:1382.**

4) deGroen PC, LeSage GD and LaRusso NF: Development and initial application of specific radioimmunoassays for rat liver lysosomal hydrolases. Gastroenterology 1983;84:1134.*

5) LaRusso NF, Novikoff PM, Novikoff AB, Stockert RJ, Yam A and LeSage GD: Immunocytochemical localization of lysosomal glycosidases in rat liver: Implications for biogenesis of lysosomal enzymes. Hepatology 1983;3:808.**

6) LeSage GD, Baldus WP and McCall JT: Estimation of hepatic iron overload by transferrin saturation, serum ferritin and chelatable iron. Hepatology 1983;3:826.*

7) LeSage GD, Kost L, LaRusso N: Colchicine, a microtubular binding agent, colchicine, augments biliary iron excretion in experimental iron overload. Hepatology 1984;4:1077.**

8) LeSage GD: Modulation of lysosomal enzyme release from cultured hepatocytes by a Ca^{++}-dependent microtubule binding agent. Gastroenterology 1985;88:1674.*

9) LeSage GD, Robertson WE. Biliary excretion of a fluid phase marker: Involvement of hepatocyte lysosomes. Hepatology 1985;5:1036.*

10) LeSage GD, Williams M: Intestinal absorption of biliary and dietary iron in normal and iron-loaded rats. Gastroenterology 1986;90(5):1741.*

11) LeSage GD, Williams M, Robertson WE: Diminished biliary excretion of lysosomal protein in experimental cholestasis. Hepatology 1986;6:1187.*

12) Holland JW, LeSage GD. Preliminary experience utilizing continuous hemofiltration in patients with fulminant failure. Southern Medical Journal 1986;79(2):16.**

13) LeSage GD, Robertson WE and Baumgart MA. Is exocytosis bile flow dependent? Gastroenterology 1987;82:1749.*

14) LeSage GD, Robertson WE and Baumgart MA. Selective alterations in hepatocyte lysosomes (HL) in cholestasis. Gastroenterology 1987;92(5):L1749.*

15) LeSage GD, Robertson WE and Baumgart MA. Bile acid-dependent secretion of lysosomal enzymes into rat bile. Hepatology 1987;7(5):1075.*

16) LeSage GD, Robertson WE and Baumgart MA. Effects of phallodin and colchicine on bile acid-dependent biliary secretion of lysosomal enzymes. Hepatology 1987;7(5):1075.*

17) LeSage GD, Kirtley DW, Culp KS and Burnett J. Does atrial natriuretic factor (ANF) affect bile flow? Hepatology 1987;7(5):1069.

18) LeSage GD, Stoltenberg PH, Kirtley DW, Culp KS and White JG. Are diminutive colorectal polyps (DCP) clinically significant? Gastrointestinal Endoscopy 1988;34:172.**

19) Kirtley DW, Stoltenberg PH, Snyder SK, Jackson JA, LeSage GD. Treatment of a duodenopancreatic fistula with a long-acting somatostatin analog (SMS 201-995). Southern Medical Journal 1988;81(9):PS24.*

20) LeSage GD, Robertson WE and Baumgart MA. Contribution of vesicular transport to bile flow. Gastroenterology 1988;94(5):A561.*

21) LeSage GD, Lasater J, Baumgarten MA and Robertson WE. Demonstration of bile acid-dependent vesicular transport by fluorescent microscopy. Gastroenterology 1989;96:A620.*

22) LeSage GD, Baldus WP and Greene JF. Phlebotomy treatment reduces hepatic fibrosis in genetic hemochromatosis. Hepatology 1989;10:576.*

23) LeSage GD, Schiller T, Hunnicutt RA, Robertson WE. Transcytosis increases bile formation in the sucrose-loaded rat. Gastroenterology 1990;98:A603.*

24) LeSage GD, Phinizy JL, Robertson WE. Organic anion transport into acidic vesicles followed by microtubule-dependent secretion into bile. Hepatology 1990;12:890.*

25) Cardenas CJ, LeSage GD. A new model for the study of portal and systemic hemodynamics in the laboratory rat. Gastroenterology 1991;100(5):A727.

26) LeSage GD, Robertson WE, Phinizy JL, Earnest KL. Organic anion transport in hepatocytes demonstrated by fluorescence recovery after photobleaching (FRAP. Gastroenterology 1991;100(5)A765.**

27) LeSage GD, Phinizy JL, Robertson WE. Microtubule-dependent biliary secretion of fluorescein but not fluorescein glucuronide. Hepatology 1991;14:255A.*

28) LeSage GD, Phinizy JL, Robertson WE, Dominguez A. Cytoplasmic and membrane-based diffusion of organic anions in hepatocyte couplets and isolated endoplasmic reticulum vesicles. Gastroenterology 1991;102:A841l.*

29) Kensing KP, LeSage GD. The effects of age and sex on hepatic lidocaine metabolism. Hepatology 1991;14:230A.*

30) LeSage GD, Phinizy JL, Dominguez A, Robertson WA. Comparison of the biliary transit time for the organic anion fluorescein to its intracellular mobility in hepatocyte couplets. Hepatology 1992;16(4):146A.*

31) LeSage GD, Phinizy JL, Dominguez A, Robertson WE. Hepatocyte intracellular microdomains and organic anion mobility. Hepatology 1992;16(4):256A.*

32) LeSage GD. Cytoplasmic and membrane-based diffusion of organic anions in hepatocyte couplets and isolated endoplasmic reticulum vesicles. Gastroenterology 1992;102(4):A840.*

33) LeSage GD, Phinizy JL, Dominguez A, Myers J. Identification and characterization of intracellular membrane-associated organic anion binding sites in rat hepatocytes. Gastroenterology 1993;104(4):A937.*

34) LeSage GD, Phinizy JL, Robertson WE, Schteingart CD, Hofmann AF. Comparison of the biliary transit time for cholylglylcyl-fluorescin to its intracellular mobility in hepatocyte couplets. Gastroenterology 1993;104(5):A937.**

35) LeSage GD, Dominguez A. Organic and inorganic anion uptake into microsomal vesicles coupled to the vacuolar H^+ATPase. Hepatology 1993;18(4):A325.*

36) LeSage GD, Schteingart CD, Hofmann AF. Effect of bile acid hydrophobicity on biliary transit time and intracellular mobility: A comparison of four fluorescent bile acid analogues. Gastroenterology 1994;106:A929**

37) G LeSage, WE Robertson, J L Phinizy, and G Alpini. Secretin stimulates genetic and functional expression of the Cl^-/HCO_3^- exchanger in rat bile duct epithelial cells. Gastroenterology 108: 1109, 1995.*

38) G Alpini, S Roberts, J L Phinizy, WE Robertson, S Gubba, O Colegio, G LeSage, and NF LaRusso. Heterogeneity of the proliferative capacity of rat cholangiocytes. Gastroenterology 109: 1025, 1995.**

39) S Gubba, S Glaser, W Robertson, J Lasater, G LeSage, and G Alpini. Compensatory cholangiocyte proliferation in rats with 70% partial hepatectomy is associated with increased ductal secretion. Hepatology 22:867, 1995.*

40) G LeSage, S Gubba, S Glaser, WE Robertson, J Phinizy, and G Alpini. Bile acids (BA) modulate proliferative and secretory capacity in large but not small cholangiocytes isolated from normal rat liver. Hepatology 22:865, 1995.*

41) I Elias, G Alpini, S Gubba, S Glaser, W Robertson, H Francis, M Richards, J Phinizy, and G LeSage. Antiproliferative effects of □-interferon in carbon tetrachloride (CCl_4)-induced cirrhosis. Hepatology 22:682, 1995.*

42) G LeSage, S Gubba, S Glaser, WE Robertson, J L Phinizy, and G Alpini. Large but not small intrahepatic bile ducts are involved in hormone-regulated bile secretion. Hepatology 22:211, 1995.*

43) S Gubba, S Glaser, W Robertson, J Phinizy, G LeSage, and G. Alpini. Cholangiocyte proliferation in rats with 70% partial hepatectomy is associated with the induction of specific growth control genes. Mol Biol Cell 6:1376, 1995.*

44) D Stagg, G Alpini, and G LeSage. Phenytoin-induced vanishing bile duct syndrome: a case report. Gastroenterology 110:1332, 1996.*

45) G Alpini, S Glaser, J Phinizy, WE Robertson, R Rodgers, J Lasater and G LeSage. Bile acid feeding stimulates proliferative and secretory events in rat cholangiocytes: evidence for bile acid-regulated ductal bile secretion. Gastroenterology 110:1141, 1996**

46) S Glaser, R Rodgers, J Phinizy, WE Robertson, J Lasater, G LeSage, and G Alpini. Gastrin inhibits secretin-induced hypercholeresis in the bile duct ligated rat liver through the cAMP system. Gastroenterology 110:1197, 1996.*

47) G Alpini, S Glaser, W Robertson, J L Phinizy, R Rodgers, and G LeSage. Large but not small intrahepatic bile duct units (IBDU) are involved in somatostatin-inhibition of secretin-stimulated ductal secretion. Gastroenterology 110:1141, 1996*

48) G LeSage, S Glaser, W Robertson, J L Phinizy, R Rodgers, and G Alpini. Partial hepatectomy induces proliferative and secretory events in small cholangiocytes. Gastroenterology 110:1250, 1996.*

49) G Alpini, S Glaser, WE Robertson, J Phinizy, R Rodgers, and G LeSage. Genetic and functional expression of the ileal Na-dependent bile acid transporter and 14 kD cytosolic bile acid binding protein in large but not small cholangiocytes from normal rat liver. Hepatology 24:513, 1996.**

50) G LeSage, S Glaser, Z Tretjiak, R Rodgers, J L Phinizy, J Lasater, WE Robertson, and G Alpini. Small cholangiocytes proliferate and repopulate hormone-responsive large ducts after CCl4-induced ductal injury. Hepatology 24:243, 1996.*

51) G Alpini, S Glaser, WE Robertson, J Phinizy, J Lasater, R Rodgers, and G LeSage. Large but not small intrahepatic bile ducts (IBDU) from bile duct ligated (BDL) rats proliferate and are involved in secretin-induced ductal bile secretion. Hepatology 24:84, 1996*

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36) Alpini G, Baiocchi L, Glaser S, Ueno Y, Marzioni M, Francis H, Phinizy JL,Angelico M, LeSage G. Ursodeoxycholate and tauroursodeoxycholate inhibit cholangiocyte growth and secretion of BDL rats through activation of PKC alpha. Hepatology. 2002 May;35(5):1041-52.

37) Kanno N, LeSage G, Phinizy JL, Glaser S, Francis H, Alpini G. Stimulation of alpha2-adrenergic receptor inhibits cholangiocarcinoma growth through modulation of Raf-1 and B-Raf activities. Hepatology. 2002 Jun;35(6):1329-40.

38) LeSage GD, Marucci L, Alvaro D, Glaser SS, Benedetti A, Marzioni M, Patel T,Francis H, Phinizy JL, Alpini G. Insulin inhibits secretin-induced ductal secretion by activation of PKC alpha and inhibition of PKA activity. Hepatology. 2002 Sep;36(3):641-51.

39) Alpini G, Glaser S, Alvaro D, Ueno Y, Marzioni M, Francis H, Baiocchi L, Stati T, Barbaro B, Phinizy JL, Mauldin J, LeSage G. Bile acid depletion and repletion regulate cholangiocyte growth and secretion by a phosphatidylinositol 3-kinase-dependent pathway in rats. Gastroenterology. 2002 Oct;123(4):1226-37.

40) Alvaro D, Alpini G, Onori P, Franchitto A, Glaser S, Le Sage G, Folli F, Attili A, Gaudio E. Alfa and beta estrogen receptors and the biliary tree. Mol Cell Endocrinol. 2002 Jul 31;193(1-2):105

41) Alvaro D, Alpini G, Onori P, Franchitto A, Glaser S, Le Sage G, Gigliozzi A, Vetuschi A, Morini S, Attili AF, Gaudio E. Effect of ovariectomy on the proliferative capacity of intrahepatic rat cholangiocytes. Gastroenterology. 2002 Jul;123(1):336-44

42) G Alpini, S Glaser, G LeSage. Bile acids stimulate proliferative and secretory events in rat cholangiocytes. Falk Bile Acid Symposium, 2002 (in press).

BOOK CHAPTERS, REVIEW ARTICLES:

1. LeSage GD "Fluid Phase Endocytosis" in Physiology and Pathophysiology, edited by N. Tavoloni and P. Berk 1993

2. L Baiocchi, G LeSage, S Glaser, and G Alpini. Regulation of cholangiocyte bile secretion. (Review). J Hepatology 31: 179-191, 1999.

3. N Kanno, G LeSage, S Glaser, and G Alpini. Functional heterogeneity of the rat intrahepatic biliary epithelium. (Review). Hepatology 31:555-561, 2000

4. G LeSage, S Glaser, and G Alpini. Regulatory mechanisms of ductal bile secretion. Digestive and Liver Diseases 32: 563-566, 2000.

5. G LeSage, S Glaser, and G Alpini. Cholangiocytes. In: Molecular Pathogenesis of Cholestasis". Michael Trauner & Peter Jansen, Eds. Landes Biosciences, Austin, Texas, USA. 2002.

6. G LeSage, S Glaser, and G Alpini. Regulation of Cholangiocyte Proliferation. Liver. 2001 Apr;21(2):73-80.

7. Baiocchi L, LeSage G, Glaser S, Alpini G. Regulation of cholangiocyte bile secretion. J Hepatol. 1999 Jul;31(1):179-91

8. Kanno N, LeSage G, Glaser S, Alpini G. Regulation of cholangiocyte bicarbonate secretion. Am J Physiol Gastrointest Liver Physiol. 2001 Sep;281(3):G612-25

9. Marzioni M, Glaser SS, Francis H, Phinizy JL, LeSage G, Alpini G. Functional heterogeneity of cholangiocytes. Semin Liver Dis. 2002;22(3):227-40.

10. G Alpini, S Glaser, and G LeSage "Bile acid interactions with cholangiocytes" in Cholangiocyte Pathobiology Alpini Alvaro LeSage and LaRusso, Eds. Landes Biosciences, Austin, Texas, USA. In press (2002)

11. M Marzioni S Glaser G LeSage, and G Alpini "Bile duct heterogeneity" In Cholangiocyte Pathobiology Alpini Alvaro LeSage and LaRusso, Eds. Landes Biosciences, Austin, Texas, USA. In press (2002)

LECTURES/CONTRIBUTIONSTO SCIENTIFIC MEETINGS:

1983 Houston, TX. University of Texas Presented "Mechanisms Of Biliary Iron Excretion In Normal And Iron Overloaded rats"

Houston, Tx Baylor College of Medicine. Presented "Genetic And Environmental Causes of Hemochromatosis"

Pittsburgh, PA University of Pittsburgh School of Medicine. Presented "Biliary Secretion of Metals By Microtubule-dependent Vesicle Pathways"

1984 Austin, TX, Presented "Evaluation of Abnormal Liver Tests". S&W and American College of Physicians sponsored Course "Gastroenterology Review

1985 Austin, TX, Presented "Evaluation of Abnormal Liver Tests". S&W and American College of Physicians sponsored Course "Gastroenterology Review

1986 Austin, TX. Presented "Alcoholic liver disease" and "Evaluation of abnormal liver tests". S&W and American College of Physicians sponsored Course "Gastroenterology review

Rochester, MN. Mayo Clinic Presented "Bile acid modulation of biliary lysosomal enzyme secretion."

1987 Austin, TX. Presented "Advances in Graft presentation in liver transplant" American College of Physicians sponsored Course "Gastroenterology review"

1988 San Antonio, TX, University of Texas at San Antonio presented "Vesicular-dependent bile formation".

San Antonio, Tx Presented "Evaluation Of Abnormal Liver Tests" American College of Physicians sponsored Course "Gastroenterology Review"

1989 Kansas City, Mo. University of Missouri at Kansas City School of Medicine. Presented "Contribution of Vesicular Transport To Bile Flow"

San Antonio, TX. Presented "Hepatic Encephalopathy: Mechanisms and Treatment" and "Evaluation Of Abnormal Liver Tests" American College of Physicians sponsored Course "Gastroenterology Review"

1990 Austin, TX Presented "Evaluation Of Abnormal Liver Tests" and "Viral Hepatitis" S&W and American College of Physicians sponsored Course "Gastroenterology Review" Yale University

1991 Woods Hole, Mass, Video microscopy "Light Microscopic Imaging Of Hepatocyte Processes"

Austin,, Tx Presented "Evaluation Of Abnormal Liver Tests" and "Viral Hepatitis" S&W and American College of Physicians sponsored Course "Gastroenterology Review"

1992 Nashville, TN. Mayo Alumni Association Annual Meeting. Presented "Hemochromatosis"

University of Texas, Austin "Video Imaging of Fluorescence Recovery After Photobleaching"

Texas A&M University College of Medicine, Department of Physiology. Presented "Organic Anion Transport Into Acidic Vesicles Followed By Microtubule-dependent Secretion Into Bile."

1993 Austin, TX Greater Austin Internal Medicine Association. Presented "New Advances In The Treatment Of Hepatitis C"

Austin, TX Presented "Liver Transplantation" and "Viral hepatitis" at S&W sponsored meeting "Gastroenterology For The Primary Care Physician"

BARGEN SYMPOSIA "Effect of Bile Acid Hydrophobicity On Biliary Transit Time and Intracellular Mobility: A Comparison Of Four Fluorescent Bile Acid Analogues"

1994 Austin, TX. Presented "Liver Transplantation" and "Liver Disease in Pregnancy" at S&W sponsored meeting "Gastroenterology For The Primary Care Physician"

Albuquerque, NM. University of New Mexico. Presented "New Advances In The Treatment Of Hepatitis C"

Midland, TX. Presented "New Advances In The Treatment Of Hepatitis C"

1995 San Antonio, TX. Presented "Hepatitis C" and "Evaluation of Abnormal Liver Tests" at S&W sponsored meeting "Gastroenterology For The Primary Care Physician

South Padre, TX. Presented "Hepatitis C" and "Evaluation of Abnormal Liver Tests" at S&W sponsored meeting "Internal Medicine Review"

THE BARGEN SYMPOSIA "Bile Acid Regulation of Cholangiocyte Proliferation and Secretion"

1996 Bargan Symposium Presented "Molecular Mechanisms in the Development of Hepatocellular Carcinoma"

Spoleto, Italy International Falk-Workshop on Vanishing Bile Duct Syndrome-Pathophysiology and Treatment". Presented "Secretin-stimulated Bile Flow in Large But Not Small Isolated Bile Duct Fragments"

San Antonio, TX. Presented "Hepatitis C" and "Evaluation of Abnormal Liver Tests" at S&W sponsored meeting "Gastroenterology for the Primary Care Physician"

University of Texas at Galveston, Presented "Identification and Characterization of Intracellular Membrane-associated Organic Anion Binding Sites in Rat Hepatocytes. "

1997 San Antonio, TX. Presented "Hepatitis C" and "Evaluation of Abnormal Liver Tests" at S&W sponsored meeting "Gastroenterology for the Primary Care Physician"

Puerto Rico, Course title: "Treatment of Hepatitis C". Presented "Hepatitis C in the Managed Care Environment".

Nashville, TN. Vanderbilt University, Presented "Heterogeneity of Proliferative And Secretory Responses In Biliary Epithelium"

1998 San Antonio, Texas. Texas Microbiology Association Annual Meeting. Presented "Molecular Mechanisms Involved in the Pathogenesis of Hepatitis B Induced Hepatocellular Carcinoma"

Chicago, IL. AASLD Research Workshop, "Cholangiocyte Pathobiology"

San Antonio Texas, Course title "Gastroenterology for the Primary Care Physician". Presented "Chronic hepatitis C" and "Abnormal Liver Function Tests"

1999 AASLD Research Workshop, Dallas TX. "Cholangiocyte Cell Biology"

Chaired Research forum "Cholangiocyte Biology" AALSD Annual meeting, Dallas, Tx

San Antonio Texas, Course title "Gastroenterology for the Primary Care Physician". Presented "Chronic hepatitis C" and "Abnormal Liver Function Tests"

2000 Den Haag, Netherlands Falk Symposium "Biology of Bile Acids in Health and Disease". Presented "Bile Acid Regulation of Cholangiocyte Growth and Secretion"

San Antonio Texas, Course title "Gastroenterology for the Primary Care Physician". Presented "Evaluation of Abnormal Liver Function Tests"

San Antonio Texas Course Title "Sexually transmitted diseases". Presented "Sexual Transmission of Hepatitis Viruses"

Chaired Research forum "Cholangiocyte Biology", Digestive Disease Week, Atlanta GA.

AASLD research workshop, Dallas TX. "Cholangiocyte Pathobiology"

2001 Airlie, Virginia NIH sponsored Single Topic Conference, Pathobiology of Biliary Epithelium, Presented "Regulation of Bile Acid Transport in Biliary Epithelium"

Baltimore, Maryland, University of Maryland School of Medicine, Presented "Regulation of cholangiocyte proliferation"

Kansas City, Ks; University of Kansas School of Medicine, Presented "Bile acid transport in biliary epithelium"

Houston, Tx; The University of Texas - Houston Medical School, Presented "Regulation of cholangiocyte proliferation"

Chaired Research forum "Cell Biology and Gene Expression" AALSD Annual meeting, Dallas, Tx

2002 Houston, TX Cholangiocyte pathobiology

University of Nebraska Presented " Getting to know the cholangiocyte"

Airlie,Virginia NIH sponsored Single Topic Conference, Biliary Atresia, Presented "Model for studying cholangiocyte biology"

J. Thomas Mortimer

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Biomedical Engineering
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Qualifications

B.S., Texas Technological College, Electrical Engineering, 1974.
Ph.D., Case Western Reserve University, Engineering, 1968.
M.S., Case Institute of Technology, Engineering, 1965.

Expertise and Research Interests

My research interest is in the area of applied neural control. Applied neural control is an emerging technology that is based on the electrical excitability phenomenon of nerve. A neural impulse can be evoked with an electrode placed near the nerve and exposing neural tissue to a pulsed electric field. This evoked response will be propagated to the nerve terminal and cause the release of a chemical substance that will in turn act on the end organ normally controlled by that nerve. Because the end organ (or body system) responds only to the incoming signal from the nerve, we have the possibility of using this technique to control any body system that is normally under the control of the nervous system; for practical purposes this is nearly the entire body. Current work focuses on electrodes and selective activation of specific neural elements and structures.

Industrial Relevance

I offer on-site short courses on electrically activating the nervous system This course is a compact version of a graduate-level course on applied neural control and is specifically designed for professionals in the neural prosthesis and neural modulation industries.

Module I. Introduction to electrically activating the nervous system, provides a starting point for understanding how electrical stimulation works for treatment of neurological impairment. Module II. Electrochemistry of stimulating electrodes, provides insight into how stimulating electrodes work, Module III. Tissue response around stimulating electrodes (brain, nerve muscle), provides insight into electrode design considerations and parameters of charge injection, and in Module IV. Selective activation techniques, techniques for future devices are developed .

Keywords

COS Keywords:

Bioelectric Phenomena, Biomedical Engineering.

Additional Terms:

Applied Neural Control, Electrical Activation of the Nervous System, Neural Prosthesis.

Languages

(Reading, Writing, Speaking)

German: (None, None, Basic)
Swedish: (None, None, Basic)

Memberships

American Association for the Advancement of Science
American Society for Engineering Education
Biomedical Engineering Society
Society for Neuroscience

Honors and Awards

2000, Electrical Engineering Academy, Texas Tech University
1996, United Cerebral Palsy Research and Education Foundation's Isabelle and Leonard H. Goldenson Technology Award, For advances in technology that improve quality of life for persons with cerebral palsy and other disabilities and their families
1992-1992, JSPS Research Fellow, Japan Society for the Promotion of Science, Tohoko University, Sendai, Japan
1976-1977, Humboldt-Preis Senior U.S. Scientist Award, Alexander von Humboldt Foundation

Previous Positions

1986-1988, Chairman, Case Western Reserve University, Computer Engineering and Science
1985-1986, Dean, Case Western Reserve University, Engineering

Patents

Customizable Interactive Texbook (CITbook, Patent Number: 6091930, 2000, Institution-owned, .
Spiral Nerve Cuff Electrode Implantation Tool, Patent Number: 6093197, 2000, Industry-owned, .
Nerve Cuff Electrode Carrier, Patent Number: 5899933, 1999, Industry-owned, .
Implantable helical spiral cuff electrode method of installation, Patent Number: 5964702, 1999, Institution-owned, .
Polymer-metal foil structure for neural stimulating electrodes, Patent Number: 5987361, 1999, Industry-owned, .
Electrode Delivery Instrument, Patent Number: 5797923, 1998, Institution-owned, .
Method of Manufacturing an Implantable Helical Spiral Cuff Electrode, Patent Number: 5689877, 1997, Institution-owned, .

Implantable Helical Spiral Cuff Electrode, Patent Number: 5505201, 1996, , .
Laprocopic Vacuum Delivery Appratus for a Diaphragm Pacer, Patent Number: 5472438, 1995, , .
Thin Film Implantable Electrode and Method of Manufacture, Patent Number: 5324322, 1994, Institution-owned, .
Double Helix Functional Stimulating Electrode, Patent Number: 5366493, 1994, Institution-owned, .
Micturitional Assist Device, Patent Number: 5199430, 1993, , Unites States of America.
"Implantable Cuff, Method of Manufacture, and Method of Installation," U.S. Patent No. 4,602,624, 1986
"Asymmetric Shielded Two Electrode Cuff, " U.S. Patent #4, 628, 942, Patented 1986
"Asymmetric Single Electrode Cuff for Generation of Unidirectionally Propagating Action Potentials for Collision Blocking," U.S. Patent No. 4,649,936, 1987
"Antidromic Pulse Generating Waveform for Collision Blocking," U.S. Patent No. 4,608,985, 1986

Publications

- Tarler, M.D, J.T. Mortimer, Comparison of Joint Torque Evoked With Monopolar amd Tripolar-Cuff Electrodes, *IEEE Trans. on Rehabilitation Engineering*, 6, 227-235, 2003
- Aiyar H, Stellato TA, Onders RP, Mortimer JT, Laparoscopic implant instrument for the placement of intramuscular electrodes in the diaphragm., *IEEE Transactions On Rehabilitation Engineering*, 7(3), 360-71, September 1999 Abstract
- Schmit BD, Mortimer JT, The effects of epimysial electrode location on phrenic nerve recruitment and the relation between tidal volume and interpulse interval., *IEEE Transactions On Rehabilitation Engineering*, 7(2), 150-8, June 1999 Abstract
- Grill WM, Mortimer JT, Stability of the input-output properties of chronically implanted multiple contact nerve cuff stimulating electrodes., *IEEE Transactions On Rehabilitation Engineering*, 6 (4), 364-73, December 1998 Abstract
- Grunewald V, Bhadra N, Creasey GH, Mortimer JT, Functional conditions of micturition induced by selective sacral anterior root stimulation: experimental results in a canine animal model., *World Journal of Urology*, 16(5), 329-36, 1998 Abstract
- Bhadra N, Mortimer J T, Extraction forces and tissue changes during explant of CWRU-type intramuscular electrodes from rat gastrocnemius., *Annals of Biomedical Engineering*, 25(6), 1017-25, November 1997 Abstract
- Grill, W.M, J.T. Mortimer, Inversion of the Current-Distance Relationship By Transient Depolarization, *IEEE Transactions on Rehabilitation Engineering*, 44, pp 1-9, 1997
- Bhadra, N, J.T. Mortimer, Extraction Forces and Tissue Changes During Explant of CWRU-Type Intramuscular Electrodes form Rat Gastrocnemius, *Annals of Biomedical Engineering*, 25:6, pp1017-1025, 1997
- Schmit, B.D, J. T. Mortimer, The Tissue Response to Epimysial Electrodes for Diaphragm Pacing in Dogs, *IEEE Transactions on BME*, 44, No, pp921-930, 1997
- Schmit, B.D., T.A. Stellato, J.T. Mortimer, Staple Penetration and Staple Histological Response for Attaching an Epimysial Electrode onto the Abdominal Surface of the Diaphragm, *Surgical Endoscopy*, 11, pp 45-53, 1997
- Grill WM, Mortimer JT, Inversion of the current-distance relationship by transient depolarization., *IEEE Transactions on Biomedical Engineering*, 44(1), 1-9, 1997 Abstract
- Grill, W.M, J.T. Mortimer, Quantification of recruitment properties of multiple contact cuff electrodes, *IEEE Transactions on Rehabilitation Engineering*, 43, pp 49-62, 1996
- Peterson DK, Nochomovitz ML, Stellato TA, Mortimer JT, Long-term intramuscular electrical activation of the phrenic nerve: safety and reliability., *IEEE Transactions on Biomedical Engineering*, 41(12), 1115-26, December 1994 Abstract

- Peterson DK, Nochomovitz ML, Stellato TA, Mortimer JT, Long-term intramuscular electrical activation of the phrenic nerve: efficacy as a ventilatory prosthesis., *IEEE Transactions on Biomedical Engineering*, 41(12), 1127-35, December 1994 Abstract
- Grill WM, Mortimer JT, Electrical properties of implant encapsulation tissue., *Annals of Biomedical Engineering*, 22(1), 23-33, 1994 Abstract
- Bonner, M.D., M. Daroux, T. Crish, J.T. Mortimer, The Pulse-Clamp Method for Analyzing the Electrochemistry on Neural Stimulation Electrodes, *Journal of the Electrochemical Society*, 141, pp2740-2744, 1993
- Fang, Z.-P, J.T. Mortimer, Selective Activation of Small Motor Axons by Quasitrapezoidal Current Pulses, IEEE Trans. BME(40), 168-174, 1991

Profile Details

Last Updated: 3/25/2004

COS Expertise ID #255946
Reference this profile directly: http://myprofile.cos.com/mortimej46

Prakash Nadkarni, M.D.

Lecturer, Yale Center for Medical Informatics

Research Interests Web Presentations Selected Publications Database Course (BIS560) Materials Microsoft Access Lecture materials

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Senior Research Investigator II
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Research Interests

My hobby (which also happens to be my job) is working with biomedical databases of all kinds.

At the moment, I'm playing with Entity-Attribute-Value (EAV) databases, which are used in domains where the number of potential descriptors (attributes) describing an object is a couple of orders of magnitude greater than the actual number of descriptors for a given object. For example, when dealing with patient data across all clinical specialties, the number of history elements,symptoms, clinical examination findings, lab tests and so on ranges in several tens of thousands, and this number is constantly growing. Yet, for a given patient, not more than a few dozen types of positive or significant negative findings are actually relevant. That is, the data is highly sparse, and a set of conventional relational tables, with one finding per column, would result in much wasted space, because most columns would be null. In the EAV approach, one stores only non-null findings in a table containing three types of information: the Entity (the patient, the date/time the finding was recorded), the Attribute (i.e., the name of the finding) and the Value of the finding.

TrialDB, an EAV database for management of Clinical Studies Data that is copyrighted by myself and my colleague Cindy Brandt (though it is open-source freeware), is described on the TrialDB Home Page. This page has an FAQ, and links to the ftp site, online documentation (also ftp-able) and the demo site where you can try it out..

I also dabble in information retrieval (a fancy phrase for text processing). This is an offshoot of my database interests: a large component of biomedical databases consists of narrative text (which captures nuances that coded text cannot):

examples are discharge summaries and operative notes. I'm looking at ways to optimize the searching process by indexing the content based on recognition of concepts in controlled biomedical vocabularies (I mainly play with the National Library of Medicine's Unified Medical Language System), and at ways of integrating text search with conventional database search.

In the past, I've worked in the area of genome informatics as well as parallel computation in molecular biology and genetics.

Presentations:

The following links point to the contents of presentations (organized as HTML framesets) that should be of general interest to medical informaticians.

Clinical Data Warehousing presented at AMIA Fall Symposium, Orlando, FL, Nov 8 1998

ACT/DB: An Infrastructure for Clinical Trials Data Management Columbia University, Jan 21 1999

The EAV/CR Physical Data Model for Heterogeneous Scientific Databases Human Brain Project Annual Meeting, NIH, Jun 5,1999

Understanding and Implementing the EAV Database in the General Clinical Research Center. National GCRC Meeting, Baltimore, MD, April 13, 2002. The URL above is a converted PowerPoint presentation. A detailed explanatory paper can be found below.

An Introduction to EAV systems: National GCRC Meeting, Baltimore, MD, April 13,2002.

Informatics Support of Data management for multi-centric clinical studies: Integrating clinical and genetics/genomic data American College of Medical Informatics, Fort Lauderdale, Florida, March 2003.

Database Representation of Phenotype Data: Issues and Challenges Human Genome Variation Society, American Society for Human Genetics Meeting, Los Angeles, CA , November 4, 2003.

Selected Publications:

Here is a list of selected recent publications. (Some of the papers are downloadable as MS-Word files plus figures, compressed into zip files. See the hyperlinks at the bottom of the publications list..)

1. Nadkarni PM. Management of Evolving Map Data: Data Structures and Algorithms Based on the Framework Map Genomics, (1995) 30:565-573.

Abstract
2. Nadkarni PM, Cheung K-H. SQLGEN: An environment for rapid client-server database development. Computers and Biomedical Research (1995) 28:479-499. Abstract
3. Nadkarni PM, Montgomery KM, Leblanc-Stracewski J, Krauter K. CONTIG EXPLORER: Interactive Exploratory Contig Assembly. Genomics (1996) 31:301-310. Abstract
4. Nadkarni PM, Cheung K-H, Castiglione C, Miller PL, Kidd KK. DNA Workbench: a database for support of regional chromosomal mapping. Journal of Computational Biology, (1996) 3 (2), 319-329. Abstract
5. Nadkarni PM. Mapdiff: an algorithm to report the differences between two genomic maps. Comput Applic Biosci, (1997) 13 (3) 217 - 225. Abstract
6. Cheung, K-H, Nadkarni PM, Silverstein S, Miller PL, Kidd KK. PhenoDB: A database for the storage and analysis of pedigree and population genetic data. Computers in Biomedical Research (1996) 79: 327-337. Abstract
7. Nadkarni PM. Concept Locator: A Client-Server Application for Retrieval of UMLS Metathesaurus Concepts Through Complex Boolean Query. Computers in Biomedical Research (1997) 30:323-336. Abstract
8. Nadkarni PM. QAV: Querying Entity-Attribute Value Metadata in a Biomedical Database.Computer Methods and Programs in Biomedicine (1997) 53 93-103. Abstract
9. Nadkarni PM. Mapmerge: merging genomic maps. Bioinformatics (1998) 14 (4), 310-316. Abstract
10. Nadkarni, P, Brandt, C, Frawley, S M, Sayward, F, Einbinder, R, Zelterman, D, Schacter, L Miller, P L. Managing attribute-value clinical trials data using the ACT/DB client-server database system. Journal of the American Medical Informatics Association (1998) 5(2) 139-151. Abstract
11. Cheung, KH, Nadkarni PM, Shin DG. A metadata approach to query interoperation between molecular biology databases. Bioinformatics (1998) 14(6) 486-497. Abstract
12. Nadkarni PM. CHRONOMERGE: An Application for the Merging and Display of Multiple Time-Stamped Data Streams. Computers and Biomedical Research (1998) 31 451-464. Abstract
13. Nadkarni, P, Brandt, C. Data Extraction and Ad Hoc Query of an Entity-Attribute-Value Database. Journal of the American Medical Informatics Association (1998) 5(6) 511-527. Abstract
14. Nadkarni PM, Marenco L, Chen R, Skoufos E, Shepherd G, Miller P. Organization of heterogeneous scientific data using the EAV/CR representation.Journal of the American Medical Informatics Association 1999 Nov-Dec;6(6):478-93. Abstract
15. Stein HD, Nadkarni P, Erdos J, Miller PL Exploring the degree of concordance of coded and textual data in answering clinical queries from a clinical data repository. J Am Med Inform Assoc 2000 Jan-Feb;7(1):42-54. Abstract
16. Nadkarni PM, Brandt C, Marenco L. WebEAV: Automatic Metadata-Driven Generation of Web Interfaces to Entity-Attribute-Value Databases. J Am Med Inform Assoc 2000;7(4):343-56 Abstract

17. Roland S. Chen, Prakash Nadkarni , Luis Marenco, Forrest Levin , Joseph Erdos and Perry L. Miller.Exploring Performance Issues for a Clinical Database Organized Using an Entity-Attribute-Value Representation. J Am Med Inform Assoc 2000; 7(5):475-487 Abstract
18. Chen RS and Brandt CA. UMLS Concept Indexing for Production Databases: A Feasibility Study. Journal of American Medical Informatics Association, 2001 8: 80-91 Abstract
19. Mutalik PG, Deshpande AM, Nadkarni PM. Use of General-purpose Negation Detection to Augment Concept Indexing of Medical Documents: A Quantitative Study using the UMLS. Journal of American Medical Informatics Association, 2001 8: 598-609 Abstract
20. Nadkarni PM: An Introduction to Information Retrieval: Applications in Genomics. The Pharmacogenomics Journal, 2002 2(2) 96-102. Abstract
21. Deshpande AM, Brandt CA, Nadkarni PM. Metadata-driven Ad hoc Query of Patient Data: Meeting the Needs of Clinical Studies. Journal of the American Medical Informatics Association. 2002; 9(4) 369-382. Abstract
22. Fisk JM, Mutalik PG, Levin FW, Erdos J, Taylor C, Nadkarni PM. Integrating Query of Relational and Textual Data in Clinical Databases: a Case Study. Journal of the American Medical Informatics Association. 2003: 10(1) 21-38.. Abstract
23. Nadkarni PM, Sun K, Wiepert M. Designing and Implementing Special-Purpose Databases: Lessons from the Pharmacogenetic Network. Pharmacogenomics 2002 3(5): 687-96. Abstract
24. Nadkarni PM. The challenges of recording phenotype in a generalizable, computable form (Perspective). The Pharmacogenomics Journal 2003 3(1) 8-10.
25. Deshpande AM, Brandt CA, Nadkarni PM. Temporal Query of Attribute-Value Patient Data: Utilizing the Constraints of Clinical Studies. International Journal of Medical Informatics 2003; 70 (1): 59-77. Abstract
26. Marenco L, Tosches N, Crasto C, Shepherd G, Miller PL, Nadkarni PM Achieving Evolvable Web-Database Bioscience Applications Using the EAV/CR Framework: Recent Advances. Journal of the American Medical Informatics Association. 2003: 10(5). Abstract
27. Brandt CA, Gadagkar R, Rodriguez C, Nadkarni PM. Managing Complex Change in Clinical Study Metadata. Journal of the American Medical Informatics Association. 2004 11(3) 380-91 Abstract
28. Marenco L, Wang TY , Shepherd G, Miller PL, Nadkarni PM QIS: A Framework for Biomedical Database Federation. Journal of the American Medical Informatics Association. 2004 11(6) 523-34. Abstract
29. Holford M, Li N, Nadkarni P, Zhao H. VitaPad: visualization tools for analysis of pathway data. Bioinformatics: 2004, 21 (8) 1596-1602 Abstract
30. Nadkarni PM and Wiepert M. Translating Pharmacogenomics Discoveries into Clinical Practice: The Role of Curated Databases Pharmacogenomics 2005 Jul;6(5):451-4.
31. Brandt CA, Argraves S, Money R, Ananth G, Trocky NM, Nadkarni PM. Informatics tools to improve clinical research study implementation.

Contemporary Clinicals Trials. 2005
32. Nadkarni PM, Brandt CA. The Common Data Elements for cancer research: remarks on functions and structure.Methods Inf Med. 2006;45(6):594-601.

Book Chapters

Shepherd, G.M., M.D. Healy, M.S. Singer, B.E. Peterson, J.S. Mirsky, L. Wright, J.E. Smith, P.M. Nadkarni, & P.L. Miller. Senselab: a project in multidisciplinary, multilevel sensory integration. pp. 21-56 of Neuroinformatics: An Overview of the Human Brain Project, ed. S.H. Koslow & M.F. Huerta. Lawrence Erlbaum Associates, Inc. Mahwah, NJ: 1997.

Prakash Nadkarni., Jason Mirsky, Emmanouil Skoufos, Matthew Healy, Michael Hines, Perry Miller and Gordon Shepherd. Modeling Heterogeneous Data on the Nervous System (Book Chapter) in Bioinformatics Databases ed. Stanley I. Letovsky. Kluwer Academic Publishers, Dordrecht , Netherlands. pp. 38-51

Books

Prakash Nadkarni: Parallel Programming with Linda: An Advanced Introduction.

Linda, conceived by David Gelernter and initially implemented by Nick Carriero, both of Yale University, is a "mini-language" constructing of just 4 constructs that is embedded in a conventional language (e.g., C or FORTRAN) to give it parallel capabilities. While conceptually very simple, its reliance on a pre-processor (that must be hand-sculpted for the language in which it is to be embedded) has limited its widespread use, by contrast with MPI, which though somewhat more difficult to use, depends purely on a subroutine library. This book was written back in 1992, and also gives an introduction to parallel programming. It can be downloaded by clicking here.

Downloadable Publications

The downloadable zip files linked to below typically contain more than one publication. Refer to the numbers in the list above. Please note: figures are generally bundled with the MS-word file, or separately, but some figures may be missing). Many of the publications have originally appeared in the Journal of the American Medical Informatics Association, from where you can get excellent content related to Medical Informatics. JAMIA publications that are more than three years old are also freely downloadable (as PDFs) from NCBI's PubMed Central Site

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publication 20
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publication 23
publication 24
publication 25
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publication 28
publication 29
publication 30
publication 32

Home

Scott L. Nyberg, M.D., Ph.D.

Minnesota

Departments

- Pediatrics
- Mayo Clinic Transplant Center

Medical School

Johns Hopkins, Baltimore, MD

Residency

General Surgery, University of Minnesota Medical School, Minneapolis, MN

Fellowship

Solid Organ Transplantation, University of Minnesota Medical School, Minneapolis, MN

Academic Rank

Professor of Surgery

Interests

Fulminant hepatic failure, artificial liver devices

Publications

See a listing of publications on PubMed, a service of the National Library of medicine.

Research

See a description of research activities.

Scott L. Nyberg, M.D., Ph.D.

Scott L. Nyberg, M.D., Ph.D.
email

- Primary Appointment
- Transplantation Surgery
- Academic Rank
- Professor of Surgery

Clinical Profile

Summary

The bioartificial liver is an important therapy developed to stabilize patients experiencing liver failure. The BAL functions outside of the patient?s body, similar to hemodialysis in the treatment of kidney failure. However, the BAL is a ?hybrid? extracorporeal device in that it contains hepatocytes, most commonly of porcine or human origin, as a biological source of liver function. My research interests are focused on the development of a multidisciplinary bioartificial liver program to improve the treatment of liver failure and support the clinical liver transplant program. A multidisciplinary liver support team exists at Mayo and this team has participated in a phase III clinical trial of the HepatAssist BAL system. We have also developed our own BAL system based on spheroid technology and expect that these studies will lead to an improved device for clinical treatment of acute liver failure.

Recent publications

See my publications on PubMed

Education

Fellowship – Solid Organ Transplantation
University of Minnesota

Chief Resident
University of Minnesota

Residency – General Surgery
University of Minnesota

Doctor of Philosophy – Biomedical Engineering
University of Minnesota

M.D.
Johns Hopkins University School of Medicine, Johns Hopkins University

B.S. – Chemical Engineering
Massachusetts Institute of Technology

NORTHWESTERN
RADIOLOGY

Directory

Reed A. Omary, MD

Associate Professor

reed@northwestern.edu

Cardiovascular Imaging, Interventional Radiology

Details

Address:	Northwestern Memorial Hospital 251 East Huron Street Feinberg 4-710W Chicago, Illinois 60611
Work Fax:	(312) 926-0826
Medical school:	Northwestern University Feinberg School of Medicine, 1991
Residency:	University of Virginia
Fellowship:	Radiology Research, University of Virginia, Charlottesville, Virginia; Cardiovascular & Interventional Radiology, Northwestern University, Chicago, Ilinois
Board certification:	Radiology, Vascular and Interventional Radiology
Interests:	Vascular and interventional radiology, MRI-guided endovascular interventions

Assistant

Name: Dorothy Woodward
Work: (312) 926-5113

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52. Omary RA, Baden JG, Becker BN, Odorico JS, Grist TM: Impact of MR angiography on the diagnosis and management of renal transplant dysfunction. J Vasc Interv Radiol 2000 Sep;11(8):991-6
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54. Frayne R, Omary RA, Unal O, Strother CM: Determination of optimal injection parameters for intraarterial gadolinium-enhanced MR angiography. J Vasc Interv Radiol 2000 Nov-Dec;11(10):1277-84
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56. Older RA, Lippert MC, Gay SB, Omary RA, Hillman BJ: Computed tomography appearance of the prostatic fossa following radical prostatectomy. Acad Radiol 1995 Jun;2(6):470-4

Department of Microbiology, Immunology and Molecular Genetics

Department:
Graduate Studies
Stipends and Fellowships
Courses
Research Areas
Seminars
Journal Clubs
Flow Cytometry

Personnel Directory:
Faculty
Admin Staff
Technical Staff
Students
Post-docs / Research Associates

Brett Spear, Ph.D.

Professor

Doctoral studies: University of Pennsylvania.

Postdoctoral: Princeton University.

Member of:
Graduate Center for Toxicology
Graduate Center for Nutritional Sciences
Integrated Biomedical Sciences (IBS) Graduate Program

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Email

Selected publications

Genomics Seminar

Research statement: My research interests are in the area of mammalian gene regulation; in particular, we are interested in transcriptional regulation in the liver during development and disease. Two experimental systems are being used for these studies. First, liver-specific regulation of the mouse alpha-fetoprotein (AFP) gene is being investigated using biochemical and molecular genetic strategies in tissue culture cells and transgenic mice. In vitro biochemical studies allow us to characterize the interplay between transcription factors and AFP regulatory elements such as the AFP promoter and enhancers. AFP constructs are analyzed in liver cell lines to further explore the consequences of these interactions. Finally, to fully understand aspects of AFP regulation, we introduce AFP DNA constructs into the mouse germline to produce transgenic animals. Using the tools and resources of the human genome project, we are also using a genetic approach to clone Afr1, a regulator of AFP expression. Our long-term objective is to understand the complex processes that control gene expression during mammalian development and will ultimately elucidate how specific organs such as the liver arise from a precursor cell population.

We are also interested in how transcription factors are involved in the response to agents that cause liver damage and/or liver cancer. In particular, we are studying the response to peroxisome proliferators, phenobarbital, and PCBs. We have focused on the link between these chemicals, oxidative stress, and the transcription factor NF-kB. Using transgenic and gene knock-out mice, we are using methods to block NF-kB activation specifically in the liver. These mice provide an in vivo model system to study the role of NF-kB in hepatocarcinogenesis and the response to liver-damaging agents.

Search COM FIND

Department of Microbiology, Immunology and Molecular Genetics

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Flow Cytometry

Personnel Directory:
Faculty
Admin Staff
Technical Staff
Students
Post-docs / Research Associates

Brett Spear, Ph.D.

Selected Publications:

Huang, M.-C., K.K. Li and B.T. Spear. 2002. The Mouse Alpha-fetoprotein Promoter is Repressed in HepG2 Hepatoma Cells by Hepatocyte Nuclear Factor-3 (FOXA). DNA Cell Biol. In press

Calfee-Mason, K.G., B.T. Spear and Howard P. Glauert. 2002. Effects of Vitamin E on the NF-kB Pathway in Rats Treated with the Peroxisome Proliferator Ciprofibrate J. Nutrition, In press

Tharappel, J.C., E. Y. Lee, L. W. Robertson, B. T. Spear, and H. P. Glauert. 2002. Regulation of Cell Proliferation, Apoptosis, and Transcription Factor Activities During the Promotion of Liver Carcinogenesis by PCBs. Toxicol. Appl. Pharmacol., 179:172-184

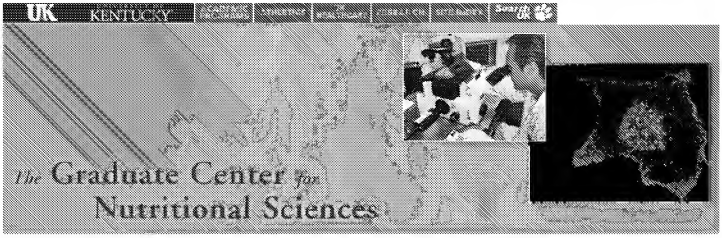
Tharappel, J.C., M.L. Cunningham, B.T. Spear, and H.P. Glauert. 2001. Differential activation of hepatic NF-kB in rats and hamsters by the peroxisome proliferators Wy-14,643, gemfibrozil and dibutyl phthalate. Toxicol. Sci. 62:20-27

Peyton, D.K., T. Ramesh, and B.T. Spear. 2000. Position-dependent activity of alpha-fetoprotein enhancer element III in the adult liver is due to negative regulation. Proc. Natl. Acad. Sci., USA. 97:10890-10894

Peyton, D.K., M.C. Huang, M.A. Giglia, N.K. Hughes, and B.T. Spear. 2000. The alpha-fetoprotein promoter is the target of Afr1-mediated postnatal repression. Genomics. 63:173-80

Spear, B.T. 1999. Alpha-fetoprotein gene regulation: Lessons from transgenic mice. Seminars in Cancer Biology. 9(2):109-116

Perincheri, S. , R.W.C. Dingle, M.L. Peterson, and Brett T. Spear (2005) Hereditary persistence of α-fetoprotein and H19 expression in liver of BALB/cJ mice is due to a retrovirus insertion in the Zhx2 gene. PNAS, 102, 396-401 [Abstract]



Research Areas
Research Facilities
Lab Photos
Seminars

Related Topics
- Faculty
- Training Grants
- Departments and Centers
- National Organizations
- Literature Search
- News

Research Areas

The Graduate Center for Nutritional Sciences benefits from the expertise of nationally and internationally known faculty with diverse areas of research expertise. Faculty members have received national research awards such as the Borden Award and Clintec Award for Nutrition Research, and serve on the editorial boards of major research journals, including the Journal of Nutritional Biochemistry.

The faculty research interest groups listed below promote faculty interaction within the same area of research interest.

Nutrition and Chronic Disease Aging

Mao, Catherine, Ph.D.
Yates, James W., Ph.D.

Obesity

Anderson, James W., M.D.
Bruemmer, Dennis, M.D.
Cassis, Lisa , Ph.D., Director
Clasey, Jodie , Ph.D.
Gong, Ming , Ph.D.
Shao, Jinhua, M.D., Ph.D.
Wang, Shuxia, M.D., Ph.D.

Cancer

Glauert, Howard, Ph.D.
Li, Guo-Min, Ph.D.
Pan, Bin-Tao, Ph.D.
Spear, Brett, Ph.D.
St Clair, Daret, Ph.D.
St. Clair, William, Ph.D.
Vanzant, Gary, Ph.D.
Zhu, Haining, Ph.D.

Cardiovascular

Bruckner, Geza, Ph.D.
Bruemmer, Dennis, M.D.
Cassis, Lisa , Ph.D., Director
Daugherty, Alan, Ph.D
de Beer, Frederick, M.D.
de Beer, Maria, Ph.D.
de Villiers, Willem, M.D.
Gong, Ming, Ph.D.
Hennig, Bernhardt, Ph.D.
Lodder, Robert, Ph.D.
Mao, Catherine, Ph.D.
Porter, Todd, Ph.D.
Post, Steven, Ph.D.
Smart, Eric, Ph.D.
Tannock, Lisa, M.D.
Toborek, Michal, M.D., Ph.D.
Van der Westhuyzen, Ph.D.
Wang, Shuxia, M.D., Ph.D.
Webb, Nancy, Ph.D.

McGowan Institute for Regenerative Medicine
A program of the University of Pittsburgh and UPMC

Stephen C. Strom, Ph.D.

Stephen Strom, Ph.D., is a Professor - Division of Cellular and Molecular Pathology at the University of Pittsburgh. His primary research interests include chemical carcinogenesis and molecular mechanisms of growth control. His primary research interests include chemical carcinogenesis and molecular mechanisms of growth control in human liver and prostate. Within his laboratory, there are two main programs under development. Under the direction of Dr. Strom, a research team is currently investigating the progression of cancer within the liver and the regulation of human gene expression.

Dr. Strom has been featured in several publications for his research efforts regarding the human liver. He has recently been recognized for his work in investigating the role of growth factors and growth factor receptor systems in the development and progression of cancer. Recent results indicate that the expression of new growth factor pathways and the communication between existing growth factor pathways are two mechanisms by which growth control regulation is lost in cancer development. In other studies, researchers have determined that the regulation of the expression of the cytochrome P450 genes in human liver is strikingly different from that observed in animal models. It has recently been identified the ethanol is a potent inducer of the CYP3A family of human genes. The induction of CYP3A by ethanol is most likely the basis for adverse effects of ethanol consumption on acetaminophen toxicity in humans. Current studies involving the examination of the promoter sequences of the human P450 genes have identified several regions of the DNA, to which protein binding can be demonstrated, which are thought to control gene expression.

CONTACT INFORMATION
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Email: strom@pitt.edu

VALENTOVIC, MONICA A, PHD
PROFESSOR
DEPARTMENT OF PHARMACOLOGY
MARSHALL UNIVERSITY SCHOOL OF MEDICINE
HUNTINGTON, WV 25755

18243470 **1:**

Related Articles, LinksRankin GO, Hong SK, Anestis DK, Ball JG, Valentovic MA.

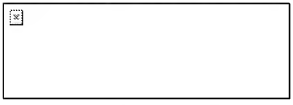
Mechanistic aspects of 4-amino-2,6-dichlorophenol-induced in vitro nephrotoxicity.

Toxicology. 2007 Dec 27; [Epub ahead of print]

PMID: 18243470 [PubMed - as supplied by publisher]

18068290 **2:**

Related Articles, LinksTerneus MV, Brown JM, Carpenter AB, Valentovic MA.



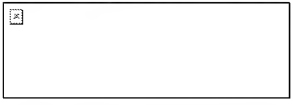
Comparison of S-adenosyl-l-methionine (SAMe) and N-acetylcysteine (NAC) protective effects on hepatic damage when administered after acetaminophen overdose.

Toxicology. 2008 Feb 3;244(1):25-34. Epub 2007 Nov 7.

PMID: 18068290 [PubMed - in process]

17728037 **3:**

Related Articles, LinksRankin GO, Anestis DK, Valentovic MA, Sun H, Triest WE.



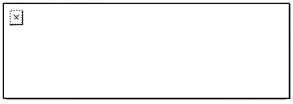
Nephrotoxicity induced by the R- and S-enantiomers of N-(3,5-dichlorophenyl)-2-hydroxysuccinimide (NDHS) and their sulfate conjugates in male Fischer 344 rats.

Toxicology. 2007 Oct 30;240(1-2):38-47. Epub 2007 Jul 20.

PMID: 17728037 [PubMed - indexed for MEDLINE]

17065366 **4:**

Related Articles, LinksTerneus MV, Kiningham KK, Carpenter AB, Sullivan SB, Valentovic MA.



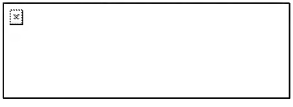
Comparison of S-Adenosyl-L-methionine and N-acetylcysteine protective effects on acetaminophen hepatic toxicity.

J Pharmacol Exp Ther. 2007 Jan;320(1):99-107. Epub 2006 Oct 25.

PMID: 17065366 [PubMed - indexed for MEDLINE]

16460892 **5:**

Related Articles, LinksValentovic MA, Alejandro N, Betts Carpenter A, Brown PI, Ramos K.



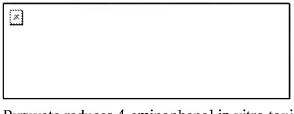
Streptozotocin (STZ) diabetes enhances benzo(alpha)pyrene induced renal injury in Sprague Dawley rats.

Toxicol Lett. 2006 Jul 14;164(3):214-20. Epub 2006 Feb 7.

PMID: 16460892 [PubMed - indexed for MEDLINE]

16343575 **6:**

Related Articles, LinksHarmon RC, Kiningham KK, Valentovic MA.



Pyruvate reduces 4-aminophenol in vitro toxicity.

Toxicol Appl Pharmacol. 2006 Jun 1;213(2):179-86. Epub 2005 Dec 15.

PMID: 16343575 [PubMed - indexed for MEDLINE]

12773762 **7:**

Related Articles, LinksValentovic MA, Minigh J.

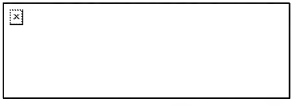
Pyruvate attenuates myoglobin in vitro toxicity.

Toxicol Sci. 2003 Aug;74(2):345-51. Epub 2003 May 28.

PMID: 12773762 [PubMed - indexed for MEDLINE]

12679054 **8:**

Related Articles, LinksMinigh JL, Valentovic MA.



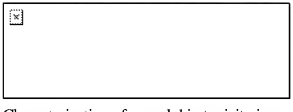
Characterization of myoglobin toxicity in renal cortical slices from Fischer 344 rats.

Toxicology. 2003 May 1;187(1):77-87.

PMID: 12679054 [PubMed - indexed for MEDLINE]

12499114 **9:**

Related Articles, LinksMinigh JL, Valentovic MA.



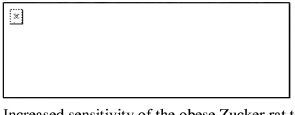
Characterization of myoglobin toxicity in renal cortical slices from Fischer 344 rats.

Toxicology. 2003 Mar 3;184(2-3):113-23. Erratum in: Toxicology. 2003 May 1;187(1):75.

PMID: 12499114 [PubMed - indexed for MEDLINE]

12409964 **10:**

Related Articles, LinksMorrison RG, Carpenter AB, Moore SK, Mangiarua EI, Valentovic MA, Walker EM Jr, Wehner PS, Rhoten WB, Touchon RC, McCumbee WD.



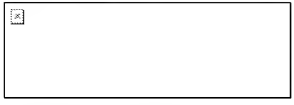
Increased sensitivity of the obese Zucker rat to deoxycorticosterone-salt-induced hypertension.

J Hypertens. 2002 Nov;20(11):2247-55.

PMID: 12409964 [PubMed - indexed for MEDLINE]

11939711 **11:**

Related Articles, LinksRankin GO, Hong SK, Anestis DK, Henderson TT, Ball JG, Valentovic MA, Brown PI,



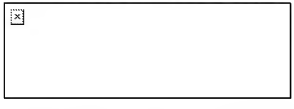
Effect of three n-acetylamino acids on N-(3,5-dichlorophenyl)succinimide (NDPS) and ndps metabolite nephrotoxicity in Fischer 344 rats.

J Toxicol Environ Health A. 2002 Apr 12;65(7):539-56.

PMID: 11939711 [PubMed - indexed for MEDLINE]

11882351 **12:**

Related Articles, LinksValentovic MA, Ball JG, Sun H, Rankin GO.



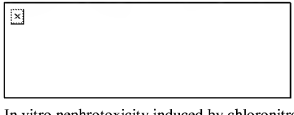
Characterization of 2-amino-4,5-dichlorophenol (2A45CP) in vitro toxicity in renal cortical slices from male Fischer 344 rats.

Toxicology. 2002 Mar 20;172(2):113-23.

PMID: 11882351 [PubMed - indexed for MEDLINE]

11879984 **13:**

Related Articles, LinksHong SK, Anestis DK, Ball JG, Valentovic MA, Rankin GO.



In vitro nephrotoxicity induced by chloronitrobenzenes in renal cortical slices from Fischer 344 rats.

Toxicol Lett. 2002 Mar 24;129(1-2):133-41.

PMID: 11879984 [PubMed - indexed for MEDLINE]

11684321 **14:**

Related Articles, LinksRankin GO, Sun H, Anestis DK, Noe O 2nd, Ball JG, Valentovic MA, Brown PI, Hubbard JL.

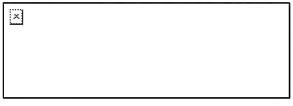
Role of stereochemistry in N-(3,5-dichlorophenyl)-2-hydroxysuccinamic acid (2-NDHSA) nephrotoxicity.

Toxicology. 2001 Nov 30;168(3):241-50.

PMID: 11684321 [PubMed - indexed for MEDLINE]

11594702 **15:**

Related Articles, LinksHong SK, Anestis DK, Valentovic MA, Ball JG, Brown PI, Rankin GO.



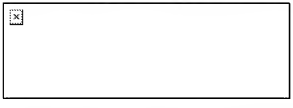
Gender differences in the potentiation of N-(3,5-dichlorophenyl)succinimide metabolite nephrotoxicity by phenobarbital.

J Toxicol Environ Health A. 2001 Oct 12;64(3):241-56.

PMID: 11594702 [PubMed - indexed for MEDLINE]

10593507 **16:**

Related Articles, LinksHong SK, Anestis DK, Ball JG, Valentovic MA, Brown PI, Rankin GO.



Sodium sulfate potentiates N-(3,5-dichlorophenyl)-2-hydroxysuccinimide (NDHS) and N-(3,5-dichlorophenyl)-2-hydroxysuccinamic acid (2-NDHSA) nephrotoxicity in the Fischer 344 rat.

Toxicology. 1999 Nov 15;138(3):165-74.

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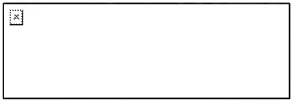

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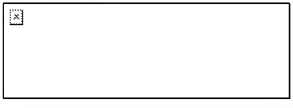

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Investigators And Their Projects » Investigator Details:

Section Info

This section contains information about all of the projects and researchers that have been funded through the Investigator Awards program since the first grants were made in 1993. The indexes in this section can be used to identify investigators by name, area of expertise, or year of award. Throughout the site, you will find that each investigator's name links to details including contact and project information.

Show details for: Wright, George

George E. Wright, Ph.D.
Associate Professor
University of Washington

Discipline: Economics; Health Services Research

Expertise: Health Services Research; Organization of Care; Rural Health Care

Email: gwright@fammed.washington.edu

Investigator Award:

Rural Models for American Health Care: Is Our Problem the Solution?

with Ira Moscovice, Ph.D.
Award Year: 2001

Rural health care is often viewed solely as a perennial problem and the object of special needs. This study takes a different perspective—many rural communities have also developed cost-effective, primary care-oriented, high-quality models that deserve careful attention. They represent America's homegrown alternative to the consolidation of health services and institutions, and to what patients often perceive as increasingly impersonal care. The investigators will test these assertions by reviewing the evidence on cost, quality, and system performance across rural areas from the viewpoint of strengths rather than weaknesses. By using small area analysis of rural health care to re-examine existing surveys, Drs. Wright and Moscovice will identify high performance systems and examine their generally lower costs. Three detailed case studies of successful models will be developed to help policymakers and administrators better understand the sources and small-scale difficulties of effective rural health care. Findings will enable the investigators to highlight lessons for improving service delivery in rural as well as urban America.

Background:

Building on a masters degree and further graduate work in Middle Eastern Area Studies, George Wright received a Ph.D. in economic development from the University of Michigan, with a dissertation on the regional dynamics of growth in Iran. He subsequently moved into health economics and worked in private sector research. Dr. Wright was a senior health economist at

SysteMetrics and then at Mathematica Policy Research, where he directed numerous studies and program evaluations for the Federal government involving rural health care. In 1996-97 he was a Fulbright Scholar teaching health policy, health economics, and economic development in Tashkent Uzbekistan, before moving to the University of Washington. Dr. Wright has been a consultant to the World Bank and AID contractors on health policy in Central Asia. Current Position: (Since 1997) Associate Professor, WWAMI Rural Research Center, University of Washington, Seattle

Selected Journal Articles:

Wright, G., Moscovice, I.. *Is Large Really Beautiful? Physican Practice in Small versus Large Scale Communities*, U of Minnesota Rural Health Research Center, Working Paper No. 56, 2005, September.

RELATED PROCEEDINGS APPENDIX

There are no proceedings related to this application or appeal.